CHAPTER 10

Posterior Pituitary

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KEY POINTS

- The posterior pituitary is neural tissue and consists only of the distal axons of the hypothalamic magnocellular neurons that make up the neurohypophysis.
- The control of hormone synthesis is at the level of transcription. Stimuli for secretion of vasopressin or oxytocin also stimulate transcription and increase the messenger ribonucleic acid (mRNA) content in the magnocellular neurons.
- The physiologic regulation of vasopressin synthesis and secretion involves two systems: osmotic and pressure/volume.
- Diabetes insipidus is a disorder of a large volume of urine (diabetes) that is hypotonic, dilute, and tasteless (insipid).
- The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is produced when plasma levels of arginine vasopressin (AVP) are elevated at times when the physiologic secretion of vasopressin from the posterior pituitary would normally be osmotically suppressed.

ANATOMY

Normal

The posterior pituitary is neural tissue and consists only of the distal axons of the hypothalamic magnocellular neurons that make up the neurohypophysis. The perikarya (cell bodies) of these axons are located in paired paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus. During embryogenesis neuroepithelial cells of the lining of the third ventricle mature into magnocellular neurons while migrating laterally to and above the optic chiasm to form the supraoptic nuclei and to the walls of the third ventricle to form the paraventricular nuclei. In the posterior pituitary the axon terminals of the magnocellular neurons contain neurosecretory granules, membrane-bound packets of hormones stored for subsequent release. The blood supply for the anterior pituitary is via the hypothalamic/pituitary portal system, but the posterior pituitary is supplied directly from the inferior hypophyseal arteries, which are branches of the posterior communicating and internal carotid arteries. The drainage is into the cavernous sinus and internal jugular vein.

The hormones of the posterior pituitary, oxytocin and vasopressin, are for the most part synthesized in individual hormone-specific magnocellular neurons, although a small number of neurons (approximately 3%) express both peptides. The supraoptic nucleus is relatively simple, with 80% to 90% of the neurons producing vasopressin and virtually all axons projecting to the posterior pituitary. The organization of the paraventricular nuclei, however, is much more complex and varies among species. In the human there are five subnuclei and parvocellular (smaller cells) divisions that synthesize other peptides, such as corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), somatostatin, and opioids. The parvocellular neurons project to the median eminence, brainstem, and spinal cord, where they play a role in a variety of neuroendocrine autonomic functions. The suprachiasmatic nucleus, which is located in the midline at the base of and anterior to the third ventricle, also synthesizes vasopressin and controls circadium rhythms as well as seasonal rhythms.

The major stimulatory neurotransmitter in the neurohypophysis is glutamate with noradrenergic stimulatory inputs acting by stimulation of glutamate. Glutamate receptors account for 25% of synapses on magnocellular neurons. The major inhibitory input is γ-aminobutyric acid (GABA), which accounts for 20% to 40% of the synaptic input to the magnocellular neurons. Phasic firing of vasopressin neurons is the most efficient activity pattern for release of vasopressin from axon terminals. Phasic activity is controlled by glutamate stimulation and opioid inhibition. Dynorphin is synthesized in vasopressin neurons and co-released with vasopressin from dendrites at the somatic level, where it acts in an autocrine fashion to inhibit the activity of the vasopressin neurons, contributing to the phasic firing pattern.

One of the most remarkable aspects of the magnocellular system is the plasticity of the system in response to prolonged stimulation. This plasticity is of greatest import in humans during parturition and lactation.

Ectopic Posterior Pituitary

With the development of magnetic resonance imaging (MRI) scans of the brain it was discovered that T1-weighted images with MRI produced a bright signal in the posterior pituitary. This allowed the identification of children in whom there was abnormal anatomy of the posterior pituitary when the bright spot was recognized in the base of the hypothalamus. These cases are referred to as ectopic posterior...
**Posterior Pituitary**

The degree of anterior pituitary deficit depends on the persistence rather than posterior pituitary deficiency. The relative deficiency of adrenocorticotropic hormone (ACTH) is common from the hypothalamus to the anterior pituitary. Deficiency of a pituitary stalk and a retained portal vasculature are recognized in children with growth retardation and anterior pituitary dysplasia. Cases with malformations are more likely to have diabetes insipidus or other osmotic dysfunction than breech delivery and perinatal injuries (these patients have a higher incidence of pituitary stalk interruption). Causes include traumatic delivery (these patients have a higher incidence of breech delivery and perinatal injuries) and genetic abnormalities of the posterior pituitary or stalk are associated with extrapituitary malformations such as septo-optic dysplasia. Cases with malformations are more likely to have diabetes insipidus or other osmotic dysfunction than simple ectopic posterior pituitary.

The latter is supported in cases in which abnormalities of the posterior pituitary or stalk are associated with extrapituitary malformations such as septo-optic dysplasia. Cases with malformations are more likely to have diabetes insipidus or other osmotic dysfunction than simple ectopic posterior pituitary. Cases are recognized in children with growth retardation and anterior pituitary deficiency rather than posterior pituitary deficiency. The degree of anterior pituitary deficit depends on the persistence of a pituitary stalk and a retained portal vasculature from the hypothalamus to the anterior pituitary. Deficiency of adrenocorticotropic hormone (ACTH) is common and should be investigated as the patients may not respond appropriately to stress.

**SYNTHESIS AND RELEASE OF NEUROHYPOPHYSEAL HORMONES**

Vasopressin and oxytocin are nonapeptides consisting of a 6–amino acid ring with a cysteine-to-cysteine bridge and a 3–amino acid tail (Fig. 10-1). All mammals have arginine vasopressin (AVP) and oxytocin, as illustrated in Figure 10-1, with the exception of the pig, in which lysine is substituted for arginine in position 8, producing lysine vasopressin. Both genes are found on chromosome 20, although they are situated in a tail-to-tail position and transcribed in opposite directions. The hormones are synthesized as part of a precursor molecule consisting of the nonapeptide and a hormone-specific neurophysin and for vasopressin a glycopeptide. The precursor is packaged in neurosecretory granules and cleaved to the products during transport to the posterior pituitary.

When a stimulus for secretion of vasopressin or oxytocin acts on the appropriate magnocellular cell body, an action potential is generated and propagates down the long axon to the posterior pituitary. The action potential causes an influx of calcium, which induces neurosecretory granules to fuse with the cell membrane and extrude the entire contents of the neurosecretory granule into the perivascular space and subsequently into the capillary system of the posterior pituitary. At physiologic pH of plasma there is no binding of hormone (vasopressin or oxytocin) to their respective neurophysins, so each peptide circulates independently in the bloodstream.

The control of hormone synthesis is at the level of transcription. Stimuli for secretion of vasopressin or oxytocin also stimulate transcription and increase the mRNA content in the magnocellular neurons. This has been studied in most detail in rats where dehydration accelerates transcription and increases the levels of vasopressin (and oxytocin) mRNA and where hypoosmolality produces a decrease in the content of vasopressin mRNA.

The transport of neurosecretory vesicles from the site of synthesis to the posterior pituitary along microtubule tracks is also regulated. When synthesis is turned off, transport stops, and when synthesis is increased, transport is upregulated. Thus, there is coordination of stimulated release of hormone, transport of hormone, and synthesis of new hormone. There is, however, asynchrony in the timing of these events. The asynchrony is demonstrated by changes in the content of vasopressin stored in the posterior pituitary. The absolute content varies considerably among species but is a remarkable store, generally equivalent to the amount of hormone required to sustain basal release for 30 to 50 days or maximum release for 5 to 10 days. In animals, prolonged and intense stimulation of vasopressin release such as dehydration or salt loading produces a depletion of stored hormone in the posterior pituitary. Then, when animals are returned to normal water intake, there is in 7 to 14 days a gradual recovery of pituitary content back to baseline. This phenomenon has been modeled by Fitzsimmons, who provided experimental evidence that a long half-life of the vasopressin message, approximately 2 days, is (from a minimalist point of view) a plausible explanation of the events. When a strong or sustained stimulus releases vasopressin there is an immediate stimulus to transcription of new mRNA. However, several days are required for the peak level of mRNA to be reached, so although release of hormone is rapid, translation increases slowly. When the stimulus is removed, the elevated mRNA slowly declines while continuing to synthesize hormone that repletes the store in the posterior pituitary.

**PHYSIOLOGY OF SECRETION OF VASOPRESSIN AND THIRST**

The physiologic regulation of vasopressin synthesis and secretion involves two systems: osmotic and pressure/volume (Fig. 10-2). The functions of these two systems are so distinct that historically it was thought there were two hormones—an antidiuretic hormone and a vasopressor hormone. Hence, the two names are used interchangeably for (8-arginine) vasopressin. There are separate systems at the level of the receptors on the end organs of response. The V1a receptors on blood vessels are distinct from V2 receptors on renal collecting duct epithelia. These two
vasopressin receptor subtypes are responsible for the main physiologic actions of vasopressin. A third receptor, \( V_{1b} \), is responsible for the nontraditional biologic action of vasopressin to stimulate ACTH secretion from the anterior pituitary and has been found in numerous peripheral tissues and areas of the brain. V2 receptors are also responsible for the nontradi- tional action of vasopressin to stimulate factor VIII and von Willebrand factor production. Vasopressin is the main hormone involved in the regulation of water homeostasis and osmolality, and the renin-angiotensin-aldosterone system (RAAS) is mainly responsible for regulation of blood pressure and volume. Pathologic disorders of the neurohypophysis are primarily expressed as abnormalities of osmolality produced by abnormal excretion or retention of water. In the case of osmoresiscusvasopressin secretion is relatively uncomplicated, with small increases in osmolality producing a parallel increase in vasopressin secretion and small decreases in osmolality causing a parallel decrease in vasopressin secretion. The regulation of volume and blood pressure is significantly more compli- cated (see review by Thrasher\(^{34}\)), and experimental models of vasopressin and baroreceptor regulation in animals often involve inhibiting and measuring other concurrent sympathetic inputs to the system in order to ascertain direct effects of any stimulus on secretion of vasopressin (see Fig. 10-2). Other influences on secretion of vasopressin such as the inhibiting influence of glucocorticoids and the potentiating influence of glucocorticoids and the potent stimulus of nausea and vomiting are less important as physiologic regulators of vasopressin but may be important in physiologic situations.

**Volume and Pressure Regulation**

High-pressure arterial baroreceptors are located in the carotid sinus and aortic arch, and low-pressure volume receptors are located in the atria and pulmonary venous system.\(^{33}\) The afferent signals from these receptors are carried from the chest to the brainstem through cranial nerves IX and X. Interruption of the vagal input by vagal cold block in dogs\(^{34,35}\) and destruction in rabbits of the A1 area of the medulla, which receives input from nerves IX and X,\(^{36-38}\) leads to an increase in vasopressin secretion. These and other data led to the concept that baroreceptors and volume receptors normally inhibit the magnocellular neurons and that decreases in this tonic inhibition result in release of vasopressin. Arterial and venous constriction induced by vasopressin action on \( V_{1a} \) receptors will contract the vessels around the existing plasma volume to effectively increase plasma volume and reestablish the inhibition of secretion of vasopressin. Vasopressin’s action at the kidney to retain water will help replace volume, but in fact, the major hormonal regulation to control volume is the RAAS, which stimulates sodium reabsorption in the kidney (see Chapter 15, The Adrenal Cortex). The concept of tonic inhibition of vasopressin secretion by baroreceptors has been questioned,\(^{39,40}\) but there is agreement that the volume/baroreceptor responses are much less sensitive than are the osmoreceptors (see Fig. 10-2). The lesser response has been attributed to the fact that changes in blood volume and central venous pressure have little effect to increase vasopressin in humans as long as arterial pressure can be maintained by alternative regulatory mechanisms such as RAAS and sympathetic reflexes.\(^{33}\) When the hypovolemia is sufficient to cause a decrease in blood pressure there is a sudden and exponential increase in the level of vasopressin in plasma\(^ {33,40}\) (see Fig. 10-2). There is also agreement that changes in volume or pressure that are insufficient to cause direct increases in vasopressin cannot nonetheless modify the response of the vasopressin system to osmoregulatory inputs.\(^ {36,41}\) Increases in pressure and central volume will decrease the secretion of vasopressin,\(^ {42}\) but again, the response of the RAAS to cause sodium excretion is much more sensitive to increases of pressure and volume than is the response to decrease secretion of vasopressin.\(^ {33}\) Consequently, changes in blood pressure and volume involve both excitatory and inhibitory influences from the brainstem to magnocellular neurons, with the dominant depending on the physiologic circumstances.

**Osmotic Regulation**

The primary receptors for sensing changes in osmolality are located in the brain. Most of the brain is within the blood-brain barrier, which is generally impermeable to polar solutes. The osmostat is insensitive to urea and glucose, which readily cross cellular membranes but not the blood-brain barrier; this provides evidence that the osmoreceptors must be outside the blood-brain barrier. Experimental brain lesions in animals have strongly implicated cells in the organum vasculosum of the lamina terminalis (OVLT) and in areas of the anterior hypothalamus near the anterior wall of the third cerebral ventricle as the primary osmoreceptors. Because these and other circumventricular organs are perfused by fenestrated capillaries, they are outside the blood-brain barrier. Surgical destruction of the OVLT abolishes vasopressin secretion and thirst responses to hyperosmolality but not their responses to hypovolemia.\(^ {43}\) Patients with brain damage that destroys the region around the OVLT cannot maintain normal plasma osmolalities even under basal conditions.\(^ {44}\) In contrast, destruction of the magnocellular neurons of the supraoptic nuclei and paraventricular nuclei eliminates dehydration-induced secretion of vasopressin but does not alter thirst, clearly indicating that osmotically stimulated thirst must be generated at a site proximal to the magnocellular cells.

Extracellular fluid (ECF) osmolality (predominantly determined by sodium concentration) varies from 280 to 295 mOsm/kg H2O in normal subjects, but in any
individual it is maintained within a narrower range. The ability to maintain this narrow range is dependent on the sensitive response of plasma vasopressin to changes in plasma osmolality; the sensitive response of urine osmolality to changes in plasma vasopressin; and then the gain in the system by the response of urine volume to change in plasma vasopressin (Fig. 10-3). Basal plasma vasopressin is in the range of 0.5 to 2 pg/mL. As little as a 1% increase or decrease in plasma osmolality will cause a rapid increase or decrease of vasopressin released from the store of hormone in the posterior pituitary. Rapid metabolism of vasopressin is also characteristic of the hormone, which circulates in plasma with a half-life of approximately 15 minutes, and this allows rapid changes in levels of vasopressin in plasma. Thus, small increases in plasma osmolality produce a concentrated urine, and small decreases produce a water diuresis. Figure 10-3 illustrates the linear relationship between plasma osmolality and plasma vasopressin that has been described in humans. This linear relationship for osmolalities persists well above the normal excursion of osmolalities as demonstrated when the increase is induced by infusion of hypertonic saline or is observed during dehydration of patients with nephrogenic diabetes insipidus. Similarly, Figure 10-3 illustrates that there is a sensitive and linear relationship between the level of vasopressin in plasma and the induced osmolality of the urine. Although plasma vasopressin may increase above the normal physiologic range, the urine osmolality plateaus at approximately 800 to 1200 mOsm/kg H₂O because the maximum concentration of fluid in the renal collecting duct is the osmolality of the inner medulla. Figure 10-3 also shows the relationship of plasma vasopressin to urine volume. This is a calculated relationship based on the urine volume necessary to excrete a fixed quantity of osmolytes (800 mOsm) at the urine osmolality produced by the change in plasma vasopressin. These graphs demonstrate the gain in the system when considering the changes in urine volume relative to plasma vasopressin. When vasopressin is absent, 18 to 20 L/day are excreted, but with an increase of vasopressin by as little as 0.5 to 1 pg/mL urine volume is reduced to less than 4 L/day. This illustrates the important point that at low plasma levels of vasopressin small changes of vasopressin are much larger determinants of polyuria than are greater changes at higher plasma levels.

In the kidney, water is conserved by the combined functions of the loop of Henle and the collecting duct. The loop of Henle generates a high osmolality in the renal medulla via the countercurrent multiplier system. Vasopressin acts in the collecting duct to increase water (and urea) permeability, thereby allowing osmotic equilibration between the urine and the hypertonic medullary interstitium. The net effect of this process is to extract water from the urine (which is removed from the medulla by interstitial blood vessels the vasa recta), resulting in increased urine concentration and decreased urine volume (antiuresis). Vasopressin produces antiuresis by binding to V₂ receptors on the epithelial principal cells of the renal collecting tubule. Binding activates adenylate cyclase, increasing cyclic adenosine monophosphate (cAMP), which then stimulates protein kinase A. This leads to phosphorylation and activation of aquaporin 2 and movement of the water channels into the luminal membrane. Aquaporin 2 is one of the widely expressed family of water channels that mediate rapid water transport across cell membranes. In the kidney, water moves from the collecting duct into the hypertonic inner medulla and produces a concentrated urine. In addition to moving constitutively synthesized aquaporin 2 from the cytoplasm to the luminal membrane,
activation of the V2 receptor also increases the synthesis of aquaporin 2 and the permeability of aquaporin 2 to water.49 Aquaporins 3 and 4 are constitutively synthesized and are expressed at high levels in the basolateral plasma membranes of principal cells, where they are responsible for the high water permeability of the basolateral plasma membrane.47,48 Dissociation of vasopressin from the V2 receptor allows intracellular cAMP levels to decrease, and the water channels are then reinternalized, terminating the increased water permeability. The aquaporin-containing vesicles remain just below the apical membrane and can be quickly shuttled into and out of the membrane in response to changes in intracellular cAMP levels. This mechanism allows minute-to-minute regulation of renal water excretion in response to changes in ambient levels of vasopressin in plasma. There is also long-term regulation of collecting duct water permeability in response to prolonged high levels of circulating vasopressin. Chronically high levels of vasopressin induce increased synthesis of aquaporin 2 and aquaporin 3 water channels in the collecting duct principal cells and hence high levels of these proteins. This response requires at least 24 hours and is not rapidly reversible. Increased numbers of aquaporin 2 and 3 water channels, combined with the effect of vasopressin to insert aquaporin 2 into the apical plasma membrane, allow the collecting ducts to achieve extremely high water permeabilities and water conservation during prolonged dehydration.47,48

**Thirst**

Urine volume can be reduced to a minimum but not completely eliminated, and insensible water loss is a continuous process. To maintain water homeostasis water must also be consumed to replace the obligate urinary and insensible fluid losses. This is regulated by thirst. Similar to vasopressin, thirst can be stimulated by increases in osmolality of the ECF or by decreases in intravascular volume. Furthermore, there is evidence that the receptors are similar, that is, osmoreceptors in the anterior hypothalamus and low- and high-pressure baroreceptors in the chest mediate the thirst stimulus (with a likely contribution from circulating angiotensin II to stimulate thirst during more severe degrees of intravascular hypovolemia and hypotension).50 Studies in humans using quantitative estimates of subjective symptoms of thirst have confirmed that increases in plasma osmolality of 2% to 3% are necessary to produce an unequivocal sensation described as “thirst.”64 Similar to vasopressin secretion, the threshold for producing thirst by hypovolemia is significantly higher.

Although osmotic changes clearly are effective stimuli of thirst, most humans consume the bulk of their ingested water as a result of the relatively unregulated components of fluid intake. Beverages are consumed with food for reasons of palatability or taken for desired secondary effects (e.g., caffeine), or for social or habitual reasons (e.g., sodas or alcoholic beverages), and as a result humans generally ingest volumes in excess of what can be considered to be an actual need for fluid. Consistent with this observation is the fact that under most conditions plasma osmolalities in humans remain within 1% to 2% of basal levels, levels generally thought to be below the threshold levels that stimulate thirst. This suggests that despite the obvious vital importance of thirst during pathologic situations of hyperosmolality and hypovolemia, under normal physiologic conditions water balance in humans is accomplished more by free water excretion regulated by vasopressin than by water intake regulated by thirst. This also explains why water intake must be consciously restricted in cases of persistent unregulated secretion of vasopressin (see later discussion of SIADH).

**Clinical Consequences of Osmotic and Volume Regulation**

In most physiologic situations there are concurrence and synergy between the effect of increased osmolality and decreased volume to stimulate release of vasopressin. For example, with dehydration osmolality increases and volume decreases and each stimulates the release of vasopressin. Furthermore, there is good evidence that a decrease in volume shifts the plasma vasopressin/plasma osmolality response curve to the left, resulting in a greater release of vasopressin at any given osmolality.51,52 Similarly, excess of fluid produces a decrease in osmolality and an increase in volume, and both will cause a decrease in vasopressin secretion.

The physiology of the relationships between plasma osmolality, plasma vasopressin, and especially urine volume determines some of the pathophysiology of decreased or increased secretion of vasopressin. Note in Figure 10-3 that a regular loss of vasopressin neurons that might decrease the secretory capacity of the neurohypophysis from that able to produce a blood level of 10 to 20 pg/mL of vasopressin down to a secretory capacity only sufficient to maintain a blood level of 5 pg/mL would not cause any significant change in the ability to attain a maximum urine osmolality. Below 5 pg/mL there is a linear decrease in the ability to maximally concentrate the urine. However, from the volume curve it can be seen that this results in only a modest increase in urine volume. Then, only when the last few vasopressinergic neurons are lost and the ability to maintain a maximum vasopressin drops from 1 to 0.5 pg/mL is there a large increase in urine volume. These responses therefore allow water conservation even with minimal ability to secrete vasopressin and may explain why patients with diabetes insipidus that has persisted for a relatively long period of time (e.g., after surgery or head injury) may eventually be able to discontinue treatment with vasopressin. The number of vasopressinergic neurons that need to recover to maintain an asymptomatic urine volume is small. The same pathophysiology is important in considering SIADH. For example, a patient who is unable to suppress vasopressin to less than 1 pg/mL can excrete 2 L/day at a standard osmolar load, but if fluid intake increases to greater than that which can be excreted with the fixed level of vasopressin, 1 pg/mL, then fluid will be retained and the sequence of events that causes hyponatremia in SIADH will be initiated.

An analysis of what is presently known about the regulation of thirst and secretion of vasopressin in humans demonstrates a simple but elegant system to maintain water balance. Under normal physiologic conditions, the sensitivity of the osmoregulatory system for secretion of vasopressin accounts for maintenance of plasma osmolality within narrow limits by adjusting renal water excretion in response to small changes in osmolality. Stimulated thirst does not represent a major regulatory mechanism under these conditions because unregulated fluid ingestion and water from metabolized food supply water in excess of true need. However, when unregulated water intake does not supply body needs even with maximal antidiuresis, plasma osmolality rises to levels that stimulate thirst, which produces water intake proportional to the elevation of osmolality. This arrangement has the advantage of freeing animals and humans from frequent episodes of thirst and water-seeking behavior when the water deficiency is sufficiently mild to be compensated for by renal
water conservation, yet it does stimulate water ingestion when water deficiency reaches a potentially harmful level.

**The Reset Osmostat During Pregnancy**

Major shifts of fluid during normal pregnancy produce a decreased plasma osmolality of about 10 mmol/kg and an increase in plasma volume and is the best example of a true resetting of the osmostat. The shift in osmotic threshold appears at about 5 to 8 weeks of gestation and persists throughout pregnancy, returning to normal by 2 weeks after delivery. The physiology of the reset osmostat has been considered in relation to the expanded plasma volume. Total body water in pregnant women is increased by 7 to 8 L as a result of profound vasodilatation. This volume is sensed as normal and vasopressin responds appropriately to decreases and increases of the expanded volume. Both the changes in volume and the changes in osmolality have been reproduced by infusion of relaxin (a normal hormone of pregnancy that is a member of the insulin-like growth factor family) into virgin female and normal male rats and reversed in pregnant rats by immunoneutralization of relaxin. Increased nitric oxide by relaxin is reported to increase vasodilatation, and estrogens also increase nitric oxide synthesis.

In women the placenta produces an enzyme, cysteine aminopeptidase, which is released into the plasma and is also known as oxytocinase. This enzyme is equally potent in degrading oxytocin and vasopressin. The activity of oxytocinase (vasopressinase) increases markedly around 20 weeks of gestation and increases further to 40 weeks, returning slowly to normal over a few weeks after delivery. The potential pathologic condition produced by oxytocinase is described later under “Diabetes Insipidus Due to Accelerated Metabolism of Vasopressin (Diabetes Insipidus of Pregnancy).”

**Osmotic Regulation in Aging**

Numerous studies have reported that elderly humans are at risk for both hyponatremia and hypernatremia. In older subjects there is a decrease in glomerular filtration rate, and the collecting duct in the aged kidney may be less responsive to vasopressin-stimulated increases in aquaporin 2 water channels, thus limiting the ability to excrete free water. Elderly subjects are reported to excrete a water load of over 4000 mL (14 oz) within 6 hours in response to an oral load of 1 L of water, whereas younger adults excrete 2000 mL (6 oz) within 6 hours. The elderly have a less responsive thirst, yet it does stimulate water ingestion when water deficiency reaches a potentially harmful level.

Diabetes insipidus is a disorder of a large volume of urine (diabetes) that is hypotonic, dilute, and tasteless (insipid). This is opposed to the hypertonic and sweet urine of diabetes mellitus (honey). Diabetes insipidus is caused by absence of the hormone vasopressin or inadequate response to vasopressin. Four syndromes of diabetes insipidus—primary polydipsia, hypothalamic/neurohypophysial diabetes insipidus, diabetes insipidus of pregnancy, and nephrogenic diabetes insipidus—can be explained, respectively, by the pathophysiology of excess intake of water, decreased synthesis or secretion of vasopressin, accelerated metabolism of vasopressin, and lack of appropriate response to vasopressin by the kidney. The absence of vasopressin produces pathologic change related only to water, not blood pressure. Most patients have an intact thirst mechanism, so they do not become dehydrated but present with polyuria and polydipsia. Patients with diabetes insipidus who have inadequate thirst can rapidly become dehydrated and develop severe hypernatremia with devastating effects on the central nervous system (CNS). Hypertonic encephalopathy with obtundation, coma, and seizures may be produced by brain shrinkage. A decreased volume of the brain in the skull may lead to subarachnoid hemorrhage, intracerebral bleeding, or petechial hemorrhage. Fortunately, problems associated with severe hypernatremia are usually not observed in patients with diabetes insipidus because of intact thirst. Hypernatremic encephalopathy is only a risk when a patient is unable to respond to thirst either because of age or level of consciousness.

To determine whether there is a large volume of urine one can measure a 24-hour urine volume, but because of the large volume it is easier in adults to keep a diary for 24 hours, recording the volume and time of each voided urine. Simultaneously, there is a determination of whether polyuria is due to an osmotic agent, such as glucose, or intrinsic renal disease. Usually routine laboratory studies and the clinical setting will distinguish these disorders from consideration of diabetes insipidus. There is universal agreement that the diagnosis of diabetes insipidus is made by some dehydration to stimulate the normal release of vasopressin but with a less than normal concentration of the urine. The gold standard is a dehydration test in a controlled environment followed by measure of vasopressin in plasma and response to administered vasopressin or the analogue desmopressin. The description that follows is for adults. Special attention is required in children and testing should be done only by a pediatrician; testing should not be done in infants. In children care should be taken to prevent hypernatremia after administration of desmopressin. The test may begin in the evening and the majority of dehydration carried out overnight. If the patient gives a history of large volumes of urine during the night, it is best to perform the test during the day when the patient can be observed.

The patient voids at the beginning of the test, and the starting weight is recorded. Serum sodium is obtained and nothing is allowed by mouth (certainly no fluid) during the test. Each voided urine is then recorded and urine osmolality measured. The patient is weighed after each liter of urine. When two consecutive measures of urine
osmolality differ by no more than 10% and the patient has lost 2% of the body weight, plasma for Na⁺, osmolality, and vasopressin is drawn and the patient is given 2 µg of desmopressin intravenously or intramuscularly. Urine output and osmolality are recorded hourly for an additional 2 hours.[4,75] The dehydration is stopped and measurements taken if the patient loses greater than 3% of the body weight or at any time that the Na⁺ is elevated above the normal range. The duration of the test varies among patients. Patients with complete diabetes insipidus reach a maximum but low urine osmolality within a few hours, but patients with other disorders may take up to 18 hours. There is no difficulty determining the diagnosis in severe hypothalamic/neurohypophyseal diabetes insipidus or severe nephrogenic diabetes insipidus. In the former, urine osmolality will have minimal concentration in spite of dehydration and there is a marked increase in urine osmolality in response to administered desmopressin, at least a 50% increase but often increasing 200% to 400%. At the end of the test these patients will have undetectable vasopressin in plasma. In nephrogenic diabetes insipidus there will similarly be little concentration of the urine in spite of achieving dehydration, but urine osmolality will also show little or no increase to administered desmopressin. Patients with nephrogenic diabetes insipidus are unequivocally distinguished from hypothalamic/neurohypophyseal diabetes insipidus by the measure of vasopressin at the end of the dehydration, often greater than 5 pg/µL.

There may be difficulty in differentiating partial hypothalamic/neurohypophyseal diabetes insipidus from primary polydipsia. With dehydration both have some concentration of the urine, often above plasma osmolality, but the urine osmolality does not approach the level of 800 to 1200 mOsm/kg that is characteristic of normal subjects. In response to the administered desmopressin patients with partial hypothalamic/neurohypophyseal diabetes insipidus usually have a further concentration of the urine, of at least 10%, whereas patients with primary polydipsia have no further increase. The reliability of the response to desmopressin is debated. Some patients with primary polydipsia may achieve a plateau level in urine osmolality before reaching their maximum urine osmolality and hence respond to desmopressin. Alternatively, some patients with partial hypothalamic/neurohypophyseal diabetes insipidus may, with severe dehydration, secrete sufficient vasopressin to achieve the maximum attainable urine osmolality and will not have a further increase to administered desmopressin. Investigators who have a highly sensitive radioimmunoassay for vasopressin are able to distinguish between partial hypothalamic/neurohypophyseal diabetes insipidus and primary polydipsia by the measure of vasopressin at the end of the dehydration test.[4,75] and further report that patients with one of these disorders may be inappropriately diagnosed as the other, using the standard dehydration test. However, a longitudinal clinical study of patients with autoimmune hypothalamic/neurohypophyseal diabetes insipidus reported good correlation between results of the dehydration test and measured vasopressin to diagnose partial diabetes insipidus.[75] When the diagnosis is in doubt, patients should have adequate follow-up to ensure that a good therapeutic response to desmopressin is obtained and that the patients do not develop hyponatremia. This clinical follow-up and response are a continuation of the diagnosis with the trial of desmopressin as a test agent. If on follow-up desmopressin produces a decrease in polyuria, a decrease in thirst, and a normal sodium concentration, the patient almost certainly has partial hypothalamic/neurohypophyseal diabetes insipidus. However, if the polydipsia does not improve and the patient develops hyponatremia, the patient has some abnormality of thirst and primary polydipsia.[6,79]

The clinical presentation is often helpful in the differential diagnosis. In a patient with onset of polyuria or polydipsia immediately after surgery in the hypothalamic/pituitary area or after head trauma (especially with skull fracture and loss of consciousness), the diagnosis of hypothalamic/neurohypophyseal diabetes insipidus is highly likely. Patients with hypothalamic/neurohypophyseal diabetes insipidus often have a sudden onset of symptoms and persistent thirst throughout the day and night associated with a desire for cold liquids.[40] Patients with diabetes insipidus usually have serum sodium in the high range of normal, and patients with primary polydipsia have serum sodium in the low range of normal. Blood urea nitrogen concentration is often low in both hypothalamic/neurohypophyseal diabetes insipidus and in primary polydipsia because of the high renal clearance, but there is a difference in serum uric acid concentrations. Serum uric acid is elevated in hypothalamic/neurohypophyseal diabetes insipidus both because of modest volume contraction and absence of the normal action of vasopressin on V₁ receptors in the kidney to increase urinary clearance. A value greater than 5 µg/dL was reported to separate hypothalamic/neurohypophyseal diabetes insipidus from primary polydipsia. Presumably in patients with primary polydipsia, there is modest volume expansion and intermittent secretion of vasopressin to act on V₁ receptors to clear serum urate.[81] Urine volume greater than 18 L is highly suggestive of primary polydipsia because this exceeds the amount of urine delivered to the collecting duct. Most patients with hypothalamic/neurohypophyseal diabetes insipidus have modest dehydration, decreased glomerular filtration rate, and urine volumes in the range of 6 to 12 L/day.

Recently there have been publications about the measure of copeptin, the glycopeptide that with neurophysin and vasopressin is part of the prohormone for vasopressin. Copeptin is secreted equimolar to vasopressin and has the advantage of being stable in plasma and more readily measurable by radioimmunoassay than is vasopressin. Although the results of clinical testing are promising, the value of copeptin as a distinguishing measure in confusing cases of diabetes insipidus (or SIADH) is still uncertain.[82]

**Imaging of the Neurohypophysis**

On T₁-weighted images the MRI produces a bright spot in the sella[2] caused by stored hormone in neurosecretory granules in the posterior pituitary.[29,85,86] The bright spot is present in approximately 80% of normal subjects[87,88] and is absent in most patients with diabetes insipidus. Some studies have reported a bright spot in patients with clinical evidence of diabetes insipidus.[89] For example, patients with familial hypothalamic/neurohypophyseal diabetes insipidus (see later) may have a bright spot early in the disease (especially when the diabetes insipidus is partial), but the bright spot disappears with increasing severity of the diabetes insipidus.[90] The role of stored oxytocin as a source of diabetes insipidus (or SIADH) is still uncertain.[90]
levels of vasopressin in plasma and are chronically dehydrated, so the posterior pituitary might be depleted of vasopressin stores. Similarly, with the osmotic stress of untreated diabetes mellitus or the transient diabetes insipidus of pregnancy the posterior pituitary may be depleted and the bright spot lost, but then it returns with recovery.\(^{91,94}\)

Imaging of the hypothalamus is also an important diagnostic tool for diseases of the neurohypophysis. As noted earlier, the hormones of the neurohypophysis are synthesized in the paired paraventricular nuclei located bilaterally in the walls of the third ventricle and supraoptic nuclei located at the extremes of the optic chiasm. Knowledge of this large area, coupled with the knowledge that 90% of the vasopressinergic neurons must be destroyed to produce symptomatic diabetes insipidus,\(^ {93,96}\) makes it apparent that for a mass lesion or a destructive lesion to produce diabetes insipidus it must either destroy a large area of the hypothalamus or be located where the tracks of these four nuclei converge at the base of the hypothalamus at the top of the pituitary stalk. Tumors confined within the sella do not cause diabetes insipidus.\(^ {90}\) The area of interest is the discrete area immediately above the sellar diaphragm. The hormones are synthesized in cell bodies and travel in axons to the posterior lobe. With section of the axons or pressure on the axons at the level of the posterior lobe there is a reaccumulation of neurosecretory material and the appearance of a posterior lobe above the site of injury.\(^ {91,97,98}\) The pituitary stalk can also be readily identified on MRI and has been an additional tool in the differential diagnosis of diseases of the neurohypophysis. Enlargement of the stalk is reported with the diseases listed in Table 10-1. When there is a diagnosis of central diabetes insipidus, thickening of the stalk is usually associated with absence of the posterior pituitary bright spot and a search for systemic diseases is indicated.\(^ {99}\) A thickened stalk with coexistent anterior pituitary deficiency is especially suggestive of etiologic disease.\(^ {100,101}\) When the cause is still in doubt, MRI should be repeated every 3 to 6 months for the first 2 years, especially in children, in whom enlargement may indicate a germinoma.\(^ {100-103}\) When follow-up shows a decrease in size of the stalk, a likely diagnosis is infundibulolymphohypophysitis.\(^ {104}\)

**Clinical Causes of Diabetes Insipidus**

**Diabetes Insipidus Due to Excess Intake (Primary Polydipsia)**

Primary polydipsia and subsequent polyuria must be differentiated from diabetes insipidus and may also contribute to SIADH. Primary polydipsia may be induced by any organic structural lesion in the hypothalamus that causes hypothalamic/neurohypophyseal diabetes insipidus (described later) and may be especially associated with sarcoidosis of the hypothalamus.\(^ {105}\) It may also be produced by drugs that cause a dry mouth or by any peripheral disorder causing an elevation of renin or angiotensin.\(^ {106}\) When there is no identifiable pathologic cause, the disorder may be associated with psychiatric syndromes or be habitual throughout a lifetime. Series of polydipsic patients in psychiatric hospitals have shown an incidence as high as 42% of patients with some form of polydipsia and for greater than half of those there was no obvious explanation for the polydipsia.\(^ {107,108}\)

**Treatment of Primary Polydipsia**

When there is no structural lesion, these patients are usually refractory to treatment.\(^ {106}\) Propranolol has been used with some success presumably because of its ability to inhibit the renin/angiotensin system.\(^ {109}\)

**Diabetes Insipidus Due to Decreased Synthesis or Secretion (Hypothalamic/ Neurohypophyseal Diabetes Insipidus)**

**Genetic Abnormalities of the Vasopressin Gene.** Hypothalamic/neurohypophyseal diabetes insipidus is characterized by the onset of classic diabetes insipidus with polydipsia and polyuria in childhood or as a young adult, but during infancy they may be asymptomatic.\(^ {130,111}\) In contrast, in familial nephrogenic diabetes insipidus the defect is expressed as a polyuric disease at birth (see later description). A rare type of familial hypothalamic/neurohypophyseal diabetes insipidus may be present at birth in infants with homozygote mutation of the AVP hormone region of the preprohormone. This may produce excretion of an inactive vasopressin but no difficulty in folding of the preprohormone.\(^ {112}\) In the usual familial hypothalamic/neurohypophyseal diabetes insipidus, MRI findings are variable even within affected family members, but the most constant finding in children is the presence of a posterior pituitary bright spot, which progressively disappears with time.\(^ {113}\) The genetic defect is usually in the biologically inactive neurophysin or in the signal peptide of the preprohormone. Although genetically heterozygous with the defect expressed in only one allele, the clinical phenotype is autosomal dominant. Lack of normal cleavage of the signal peptide from the prohormone and abnormal folding of the vasopressin/neurophysin precursor are thought to produce fibrillar aggregations in the endoplasmic reticulum, which is cytotoxic to the neuron, explaining the dominant phenotype.\(^ {114,115}\) Autopsy studies have confirmed neuronal cell death.\(^ {116}\) Genetic testing of asymptomatic children in affected families will negate the need for repeated dehydration testing and allow early treatment.\(^ {117}\) Wolfram syndrome is a rare autosomal recessive disease with diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD). The genetic defect is for the protein wolframin that is found in the endoplasmic reticulum and is important for folding proteins.\(^ {118}\) Wolframin is localized to chromosome 4. It is involved in beta-cell proliferation and intracellular protein processing and calcium homeostasis, producing a wide spectrum of endocrine and CNS disorders. Diabetes insipidus is usually a late manifestation and is associated with decreased magnocellular neurons in the paraventricular and supraoptic nuclei.\(^ {113,119}\)

**Malignancies.** Some tumors such as craniopharyngioma and primary germ cell tumors in children characteristically occur in a suprasellar basal hypothalamic area and are

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TABLE 10-1

<table>
<thead>
<tr>
<th>Diseases Associated With Enlarged Infundibular Stalk</th>
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<tbody>
<tr>
<td>1. Germinoma</td>
</tr>
<tr>
<td>2. Craniopharyngioma</td>
</tr>
<tr>
<td>3. Metastases to the hypothalamus and long portal vessels (e.g., carcinoma of the breast or lung)</td>
</tr>
<tr>
<td>4. Granulomatosis diseases</td>
</tr>
<tr>
<td>a. Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>b. Sarcoïdosis</td>
</tr>
<tr>
<td>c. Wegener granulomatosis</td>
</tr>
<tr>
<td>d. Non–Langerhans cell histiocytosis (e.g., Erdheim-Chester disease)</td>
</tr>
<tr>
<td>5. Tuberculosis</td>
</tr>
<tr>
<td>6. Lymphoïcystic infundibulohypophysitis</td>
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</tbody>
</table>
regularly associated with diabetes insipidus. It is not uncommon for diabetes insipidus to be the presenting complaint, although other evidence of hypopituitarism is often present. The MRI often shows a thickened stalk and may show a hypothalamic mass. Tumor markers in plasma or cerebrospinal fluid (CSF) may confirm the tumor type in children, but absence of markers does not rule out any specific cause.

Metastatic disease involving the pituitary is usually found in association with widespread metastatic disease and may be asymptomatic and only reported at autopsy. Metastases are twice as likely to involve the posterior pituitary as the anterior pituitary, and this is thought to be due to a more direct arterial blood supply to the posterior pituitary. Most primary tumors in the hypothalamic/pituitary area that cause diabetes insipidus are relatively slow growing, and any tumor in this area that shows rapid growth in a short period of time should be considered as a possible metastatic tumor. Pituitary abscess is a rare cause of a pituitary mass and diabetes insipidus. Diabetes insipidus is reported with lymphomas in the hypothalamic/pituitary area. There may be some increased incidence of lymphoma presenting with diabetes insipidus due to the increased incidence lymphoproliferative disease with human immunodeficiency virus (HIV) and hepatitis C infection. Diabetes insipidus is also associated with leukemia. The mechanism is thought to be infiltration of the hypothalamus, thombosis, or infection. Diabetes insipidus is distinctly more common in nonlymphocytic leukemia. MRI studies in leukemia may show infiltration or an infundibular mass but often are normal even when leukemic cells are found in the CSF.

Granulomatous Diseases. In most cases of diabetes insipidus caused by granulomatous disease there is clear evidence of characteristic disease elsewhere in the body. The MRI will show involvement of the hypothalamus and absence of the posterior pituitary bright spot on T1-weighted images with widening of the stalk (see Table 10-1). Although there are occasional reports of resolution of the diabetes insipidus with appropriate therapy of the primary disease, in most cases, once it is established, diabetes insipidus is permanent.

Infundibulohypophysitis. The forms of lymphocytic hypophysitis are classified by the tissues as adenohypophysitis, infundibuloneurohypophysitis, or panhypophysitis and may extend into the hypothalamus. All of these forms are usually associated with a thickened stalk and loss of the pituitary bright spot on T1-weighted MRI. Adenohypophysitis often involves females around the time of a pregnancy, whereas infundibuloneurohypophysitis occurs in either sex. A recently recognized form of infundibuloneurohypophysitis occurs in middle-aged to elderly males and is associated with immunoglobulin G4 (IgG4)-related systemic disease. Various organs, especially the pancreas, are infiltrated with IgG4 plasma cells, and neurohypophysitis is only one manifestation of a multiorgan disease that may include other endocrine glands. This finding should be considered as a cause of diabetes insipidus based on age and sex at presentation and evidence of other systemic disease. The diagnosis can be established by elevated serum IgG4 level and characteristic histologic findings on biopsies. Response to steroids or other immunosuppressive drugs is characteristic. When a definitive cause of diabetes insipidus is not found, most cases of diabetes insipidus will be labeled idiopathic, but an autoimmune process should always be considered.

Surgery or Trauma of the Neurohypophyseal System. Although diabetes insipidus is well known to occur after hypothalamic or pituitary surgery, this diagnosis should be made with caution. Vasopressin is normally secreted in the stress of surgical procedures and fluid may be retained, which is then excreted normally after surgery. Stress of surgery may also induce insulin resistance and exacerbate diabetes mellitus, producing an osmotic diuresis from glucose. The patterns of diabetes insipidus after surgery have been described in detail. As many as 50% to 60% of patients will have some transient diabetes insipidus within 24 hours of pituitary surgery, and it will usually resolve (especially with transsphenoidal surgery in which the resection of a tumor is confined to the sella), with only a small number having permanent diabetes insipidus. The introduction of endoscopic pituitary surgery has not increased the incidence of diabetes insipidus, and there continues to be greater morbidity with surgery for craniopharyngioma.

If there is complete stalk section patients may exhibit a pattern known as triphasic diabetes insipidus (Fig. 10-4). The first phase is diabetes insipidus with onset within the first 24 hours of surgery and is thought to be due to axon shock and inability of action potentials to be propagated from the cell body to the axon terminals in the posterior pituitary. The second phase is an antidiuretic phase, which was originally described as a normal interphase but is not normal and is thought to be due to unregulated release of vasopressin from the store of hormone in the degenerating axons of the posterior pituitary. Because the release of vasopressin in this phase is unregulated, excess administration of fluids will produce hyponatremia and SIADH. When the entire hormone content has been released diabetes insipidus returns, constituting the third phase. The course of diabetes insipidus may be permanent, or subsequently it may resolve to partial or clinically inapparent disease.

An important observation is that the second phase of the triphasic response (i.e., uncontrolled release of vasopressin due to axon trauma) may occur without preceding diabetes insipidus. This isolated phase has been reported clinically and has been produced experimentally in the rat by unilateral lesion of the supraopticohypophyseal tract. The interpretation is that if the trauma has involved only some of the axons coursing to the posterior pituitary, then the remaining intact axons

![Figure 10-4 Typical triphasic response of urine volume after sectioning of the pituitary stalk induced by surgery or head trauma. The first phase of diabetes insipidus occurs immediately postoperatively and continues to day 6. The second phase of antidiuresis occurs from day 7 and continues to day 12. The third stage is the recurrence of diabetes insipidus on day 13. Durations vary; see text for detailed discussion.](From A.G. Robinson, University of California at Los Angeles, used with permission.)
will have sufficient vasopressin function to avoid the clinically apparent diabetes insipidus that is characteristic of the first and third phases of the triphasic response. However, the store of hormone in the posterior pituitary is sufficiently large that necrosis of even a fraction of these vasopressin neurons will cause enough uncontrolled release of vasopressin to produce hyponatremia if excess fluid is administered. The hyponatremia is often symptomatic, and patients present with headache, nausea, and emesis or seizure. When all the vasopressin from the damaged neurons has been secreted the stimulus for water retention resolves and the retained water is excreted, producing recovery from the hyponatremia. Thus, the clinical picture is one of hyponatremia occurring around 7 to 10 days after pituitary surgery, persisting for a few days, and then returning to normal. This syndrome of transient hyponatremia has been referred to as isolated second phase to emphasize the pathophysiologic cause. Isolated hyponatremia has been reported in 10% to 25% of patients after pituitary surgery.

The same patterns of diabetes insipidus that occur after surgery can be seen in patients after closed-head trauma, and the incidence may be increasing because of better care and increased survival of patients with severe head injury. Patients with penetrating injury and children are especially at risk. Three quarters of these cases are due to motor vehicle accidents. Computed tomography or MRI in a large group of patients with posttraumatic hypopituitarism including diabetes insipidus revealed hemorrhage in the hypothalamus or posterior pituitary in 55% of patients, and approximately 5% of patients had stalk resection or infarction of the posterior pituitary.

There are several important clinical points to be made with regard to diabetes insipidus induced by head trauma. First, these patients are virtually always unconscious and will not have the normal ability to sense thirst. Second, it is a situation in which large volumes of fluid might be given because of blood loss or other volume deficits, and this fluid loss or stress might induce diabetes mellitus and an osmotic diuresis. Third, there may be a greater risk if the second phase is unrecognized because hyponatremia will produce cerebral edema, which may aggravate any edema due to trauma. Therefore, in administering desmopressin the effect of one dose should be allowed to wane before administering another dose to ensure that the patient has not entered the second phase.

There is a high incidence of anterior pituitary deficiency in association with diabetes insipidus induced by head trauma. The possibility of cortisol deficiency should be considered immediately because this problem may be life threatening in these patients. Cortisol deficiency should also be considered subsequently if diabetes insipidus appears to improve because of decreased polyuria. Cortisol deficiency alone decreases the ability to excrete water even in the absence of vasopressin. Last, in a long-term follow-up of these patients partial diabetes insipidus may be found, and there may be return of sufficient vasopressin function that under basal conditions the patient is no longer symptomatic from a large urine output.

**Absent Release of Vasopressin and Absent Thirst in Response to Osmotic Stimulation.** Lack of thirst in response to increased osmolality indicates an abnormality of the osmostat. This may be seen in hypothalamic/neurohypophyseal diabetes insipidus when the initial lesion or surgical damage is so severe that the damage is not only to the neurohypophysis but also to the central anteriorly placed osmostat or with isolated damage of the osmostat with intact baroreceptors described as essential hypernatremia. In the former there is no release of vasopressin in response to either osmotic or baroreceptor stimulation, but in the latter there is adequate synthesis of vasopressin and release with baroreceptor stimulation but no release with osmotic stimulation. Massive damage of the hypothalamus is necessary for the former and is most commonly seen in patients with craniopharyngioma or a pituitary tumor with extremely large suprasellar extension, often with anterior pituitary deficiencies and other manifestations of hypothalamic syndrome (e.g., hyperphagia, sleep apnea, thermoregulation, seizures). Abnormalities of thirst with primary hypothalamic lesions are most common with sarcoidosis, but the pattern of essential hypernatremia with absent osmostat and intact baroreceptor is most commonly reported after clipping of an anterior communicating artery aneurysm. In these cases there is evidence that vasopressin is synthesized and stored in that maneuvers to stimulate baroreceptors increase secretion of vasopressin and concentration of the urine. The pathophysiologic explanation of essential hypernatremia is that inadequate water intake and excess water excretion produce a degree of dehydration with hypernatremia; when the dehydration is sufficient to stimulate the baroreceptors, vasopressin is released, urine is concentrated, and the patient remains in a steady state of hypernatremia with modest dehydration. The increased concentration of sodium per se also causes sodium excretion to help maintain the new steady state.

**Diabetes Insipidus and Brain Death.** Diabetes insipidus is reported in 50% to 90% of patients with brain death. Although some aspects of hormonal treatment of organ donors are controversial, there is consensus that treatment of diabetes insipidus should be standard in donors with this disorder.

**Treatment of Hypothalamic/Neurohypophyseal Diabetes Insipidus**

**Mass Lesions of the Neurohypophysis: Malignancies, Granulomas, Infundibulitis.** A major goal of therapy is to decrease the thirst and polyuria to a level that allows the patient to maintain a normal lifestyle. The timing and quantity of dosage should be individually prescribed and easy for the patient to accommodate. Safety of the prescribed agent and avoiding detrimental effects of overtreatment are primary considerations because of the relatively benign course of diabetes insipidus and the adverse consequences of hypernatremia. The therapeutic agents to treat diabetes insipidus are shown in Table 10-2. Water is considered a therapeutic agent because when taken in sufficient quantity there is no metabolic abnormality. Therapy is designed to reduce the

**TABLE 10-2**

**Therapeutic Agents for Treatment of Diabetes Insipidus**

<table>
<thead>
<tr>
<th>1. Water</th>
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<tbody>
<tr>
<td>2. Water-retaining agents</td>
</tr>
<tr>
<td>a. L-Arginine vasopressin</td>
</tr>
<tr>
<td>b. Desmopressin, 1-3-mercaptopropionic acid-D-arginine vasopressin</td>
</tr>
<tr>
<td>c. Chlorpropamide</td>
</tr>
<tr>
<td>d. Carbamazepine*</td>
</tr>
<tr>
<td>e. Clofibrate*</td>
</tr>
<tr>
<td>f. Indomethacin</td>
</tr>
<tr>
<td>3. Natriuretic agents</td>
</tr>
<tr>
<td>a. Thiazide diuretics</td>
</tr>
<tr>
<td>b. Amiloride</td>
</tr>
<tr>
<td>c. Indapamide</td>
</tr>
</tbody>
</table>

*Not recommended.
necessary water intake (and polyuria) to an acceptable level, but occasional lapses in pharmacologic therapy are not detrimental, may avoid overtreatment producing hyponatremia, and allow recognition of any spontaneous recovery.

The drug of choice is desmopressin, a synthetic analogue of vasopressin in which the substitution of D-arginine markedly reduces pressor activity and removing the terminal amine increases the half-life (see Fig. 10-1). The two changes produce an agent nearly 2000 times more specific for antidiuresis than naturally occurring L-arginine vasopressin. Desmopressin is available as tablets for oral administration, a lyophilisate for sublingual administration (oral melt), a solution for intranasal administration, and a solution for parenteral use. Most patients prefer desmopressin tablets (0.1 and 0.2 mg), although many patients continue to be successfully treated with the intranasal spray. Desmopressin melt (60, 120, and 240 µg) is reported to be more acceptable in some children. Because of the variability among patients it is desirable to determine the duration of action of individual doses in each patient. The patient is first allowed to escape from the effects of any previous medication, and for each voided urine the time and volume are recorded and, if possible, osmolality is measured. A dose of desmopressin is given and the patient is allowed to drink fluid ad lib. A decrease in urine volume is noted in 1 to 2 hours, and the total duration of action will usually be 6 to 18 hours. When a dose is sufficient to elicit a stable therapeutic response, further increasing the dose (e.g., doubling the dose) produces only a moderate increase in duration of a few hours, consistent with the half-life of desmopressin in plasma. Usually a satisfactory schedule is achieved with a modest dose and the maximum dose rarely exceeds 0.2 mg orally or 20 µg intranasally (two sprays) given two or three times a day (usually three times a day for tablets and twice for intranasal spray). Using the tablets allows considerable flexibility in dosage by using either whole or split tablets. For intranasally administered desmopressin there is less flexibility with the metered spray, which is fixed at 10 µg in 100 µL. For greater flexibility with intranasal administration the patient may be taught to use the rhinal catheter. Specific directions are described elsewhere. Rarely is it necessary to resort to parenterally administered desmopressin (2 mL vials of 4 µg/mL) for ambulatory patients. If an intercurrent illness or allergy makes this desirable, a dose of 0.5 to 2.0 µg can be administered subcutaneously using an insulin (low dose if necessary) syringe and needle. Parenterally administered desmopressin gives virtually identical therapeutic response when given as an intravenous bolus, intramuscularly, or subcutaneously, and the parenteral administration is 5 to 20 times as potent as an intranasally administrated dose. Recent studies have reported an increased antidiuretic response to desmopressin in women and in the elderly.

The therapeutic agents listed in Table 10-2 that induce water retention have other clinical indications and when used in patients with diabetes insipidus might augment the effect of administered desmopressin, exposing the patient to excess water retention and hyponatremia. This effect may be especially true of over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the action of prostaglandin E₂. Prostaglandin E₂ has a limiting action on vasopressin-induced water uptake by enhancing the retrieval of aquaporin 2 from the plasma membrane and returning it to the intracellular pool. NSAIDs inhibit prostaglandin E₂ and prolong the time the water channels remain in the membrane, thus increasing the duration of action of administered desmopressin. Hyponatremia is a rare complication of desmopressin therapy and only occurs if the patient is continually antidiuretic while maintaining a fluid intake sufficient to become volume expanded and natriuretic. Thirst may be protective; most patients on standard therapy are not continuously maximally antidiuretic or may occasionally delay a dose to excrete any excess retained water. Treatment of infants requires special attention and expertise. Infants consume a large part of their calories as liquid formula or breast milk and have corresponding high volume of dilute urine. Treatment with oral or intranasal desmopressin is reported to have broad swings of the serum sodium and the risk of symptomatic hyponatremia. In Europe a lyophilisate of desmopressin is used orally and in the United States pediatricians have used desmopressin subcutaneously or substituted a low solute formula with a thia-zide diuretic. In the earlier discussion of physiology it was noted that normal elderly persons have reduced ability both to concentrate their urine and to excrete a water load. Therefore, treatment of an elderly patient with diabetes insipidus requires special attention to avoid hyponatremia. Because elderly persons may have an increased use of NSAIDs, patients with diabetes insipidus should be specifically informed of the risk of developing hyponatremia when taking an NSAID with desmopressin. Diabetes Insipidus After Hypothalamic or Pituitary Surgery or Injury. The surgeon often knows how severely the posterior pituitary or stalk was injured. Sometimes diuresis after surgery is the result of water retention during the procedure. Vasopressin is released during surgical procedures, and administered fluid may be retained. When the stress of surgery abates the vasopressin level falls and retained fluid is excreted. If an attempt is made to match the urine output with further fluid infusion, persistent polyuria might be mistaken for diabetes insipidus. If in doubt, fluid can be withheld until there is a modest increase in sodium. If the urine output decreases and the serum sodium remains normal, the polyuria was due to excretion of physiologically retained fluid. If the serum sodium begins to rise while urine osmolality is low and there is a positive response to administered desmopressin, the diagnosis of diabetes insipidus can be established. Sometimes the duration of diabetes insipidus is quite transient and the surgeon may prefer to treat it only with fluid replacement parenterally or orally (if the patient is awake and able to respond to thirst). In treating diabetes insipidus desmopressin may be given parenterally 0.5 to 2 µg, subcutaneously, intramuscularly, or intravenously. The intravenous route may be preferable because there is no question about absorption. Urine output will be reduced in 1 to 2 hours and the duration of effect is 6 to 24 hours. If the patient is alert, thirst is a good guide to fluid replacement. Care should be taken that intravenous fluids (especially hypotonic) are not given excessively after administering desmopressin because this practice can lead to profound hyponatremia. As the
diabetes insipidus may be quite transient and some of these patients may develop the triphasic pattern described previously, it is desirable to allow polyuria to return before administering subsequent doses of desmopressin.151

Treatment of acute diabetes insipidus after blunt trauma to the head can be similar to postoperative care, except that the patient with head injury is more likely to be comatose and unable to respond to thirst and therefore is more likely to develop hypernatremia. Because a comatose patient must be given fluids parenterally some clinicians prefer to use a continuous infusion of low-dose vasopressin. The vasopressin can be added directly to the crystalloid solution that is being administered185 or can be infused separately to maintain a constant antidiuresis while adjusting the fluid intake appropriate to any persistent polyuria and to cover insensible water loss. Doses of 0.25 to 2.7 μU/kg/hour have been described.189,190 If this method is used, there is a potential to produce hyponatremia,188,189 and serum sodium must be checked regularly. Of course, with continuous replacement one will not know whether there is return of normal function or whether a patient might be entering the second phase of the triphasic pattern described earlier.

Diabetes Insipidus With Inadequate Thirst. The high incidence of anterior pituitary deficiency in these patients should be considered in any treatment of diabetes insipidus.192 With lack of thirst and continuing polyuria these patients will develop severe hypernatremia; if they are encouraged to drink and an antidiuretic agent is administered, they are at risk for hyponatremia. Therefore, these patients are subject to wide swings in osmolality, but most characteristically, they have persistent hypernatremia. The first therapeuetic agent that might be tried is chlorpropamide off label because it is useful to treat diabetes insipidus and has been reported to increase the thirst response.193,194 Again, this is off-label use of chlorpropamide. If chlorpropamide does not produce adequate control, treatment involves balancing desmopressin and fluid intake. The patients are not thirsty and it is difficult to balance water intake, so a better regimen is a rigid fixed dose of desmopressin to maintain chronic antidiuresis and a prescribed quantity of water that must be drunk every 6 to 8 hours.167,195 Daily weight can be used to guide intake, and regular follow-up with measurement of serum sodium is essential to assure that these patients do not develop water intoxication with hyponatremia or recurrent dehydration with hypernatremia. This balance may be especially difficult to manage in infants. Desmopressin by injection and careful management of fluids with regular measurement of sodium have been used successfully.196

Organ Donors. As noted earlier, diabetes insipidus is a common accompaniment of brain death, and if these patients are candidates for organ donation, it has been suggested that maintaining fluid homeostasis is desirable for maintenance of the health of the organs. Continuous administration of low-dose vasopressin intravenously as described earlier for postsurgical diabetes insipidus may be easier than maintaining antidiuresis with intermittent doses of desmopressin.

Diabetes Insipidus Due to Accelerated Metabolism of Vasopressin (Diabetes Insipidus of Pregnancy)

An important clinical point is the expanded volume and decreased osmolality and serum sodium that occur in normal pregnancy, as described earlier in the discussion of physiology. Pregnant patients with polyuria may have serum sodium levels that would be in the normal range for a nonpregnant patient but would be indicative of diabetes insipidus in the pregnant patient and require evaluation. There are two types of transient diabetes insipidus in pregnancy, both caused by the enzyme cysteine aminopeptidase (oxytocinase).197 In the first type the activity of cysteine aminopeptidase (which is also a vasopressinase) is extremely and abnormally elevated. This syndrome has been referred to as vasopressin-resistant diabetes insipidus of pregnancy.198 It occurs with preeclampsia, acute fatty liver, and coagulopathies (e.g., HELLP [hemolysis, elevated liver enzymes and low platelets] syndrome). These patients have decreased metabolism of vasopressinase by the liver.53,199,201 Usually in subsequent pregnancies these women have neither diabetes insipidus nor acute fatty liver. In the second type the accelerated metabolic clearance of vasopressin produces diabetes insipidus in a patient with borderline vasopressinase function from a specific disease, such as mild nephrogenic diabetes insipidus or partial hypothalamic/neurohypophyseal diabetes insipidus.202 Vasopressin is rapidly destroyed and the neurohypophysis is unable to keep up with the increased demand. Labor and parturition usually proceed normally, and patients have no trouble with lactation.204 When diabetes insipidus is unrecognized in a pregnant woman, chronic and severe dehydration may pose a threat.205 Patients with Sheehan syndrome have been reported to have asymptomatic partial diabetes insipidus,206 but they rarely develop overt diabetes insipidus.207

Treatment of Diabetes Insipidus in Pregnancy

Desmopressin is the only therapy recommended for treatment of diabetes insipidus during pregnancy. Desmopressin has 2% to 25% the oxytocic activity of lysine vasopressin or AVP192 and can be used with minimal stimulation of the oxytocin receptors in the uterus.201,204,208 The physician must note the naturally occurring volume expansion and the reset osmostat that occur in pregnancy and give sufficient therapy to satisfy thirst and to maintain a serum sodium at the low level that is normal during pregnancy. Desmopressin is not destroyed by the cysteine aminopeptidase (oxytocinase) of pregnancy204,209 and is reported to be safe for both the mother and the child.210,211 During delivery these patients can maintain adequate oral intake and continue administration of desmopressin. Physicians should be cautious about overadministration of fluid parenterally during delivery because these patients will not be able to excrete the fluid and may develop water intoxication and hyponatremia. After delivery oxytocinase decreases in plasma and the patient may recover completely or be asymptomatic with regard to volume of fluid intake and urine excretion.

Diabetes Insipidus Due to Lack of Renal Response (Nephrogenic Diabetes Insipidus)

Genetic Abnormalities. Infants with nephrogenic diabetes insipidus present with vomiting, constipation, failure to thrive, fever, and polyuria. Symptoms usually occur during the first week of life,212,213 and on testing the patients will be found to have hyponatremia and a low urine osmolality. The diagnosis is established by high levels of vasopressin in the plasma in the presence of hypotonic polyuria and then the absence of response to administered desmopressin. Special attention should be given if a dehydration test is used in children and the test should not be done in infants. Care should be taken to avoid hyponatremia when desmopressin is given at the end of the test as hypotonic fluid is the normal diet.204 Considered here are disorders related directly to function of vasopressin, and no other
inherited complex disorders of the kidney that cause loss of electrolytes as well as water.714 Two causes of nephrogenic diabetes insipidus are mutations in the V2 receptor and mutations of the aquaporin 2 water channels. The presentation is independent of the genotype.122-124

More than 90% of cases of nephrogenic diabetes insipidus are X-linked recessive disorders in males who have one of more than 200 individually different mutations of the V2 receptor.223 Three classes of mutations of the V2 receptor have been described: type 1 disorders reach the cell surface but have impaired AVP binding; type 2 have defective transport and remain in the cell without reaching the cell surface; and type 3 are unstable and rapidly degraded.215 Most of the reported cases are type 2.216 In clinical series approximately 10% of the V2 receptor defects causing congenital nephrogenic diabetes insipidus are thought to be de novo. Although most female carriers of the X-linked V2 receptor defect have no clinical disease, some female carriers may have a decreased maximum urine osmolality in response to the plasma level of vasopressin that they achieve.217 Rarely, heterozygous females have a defect as severe as males and this is thought to be due to inactivation of the normal X chromosome.218,219

When the proband is a female it is likely that the defect is a mutation of the aquaporin 2 water channel gene producing an autosomal recessive disease.220 This should be especially considered when consanguinity is known in the family and the disease is expressed in males and females. The patients may be heterozygous for two different recessive mutations221 or may be homozygous for the same abnormality from both parents.222 Mutations of the aquaporin 2 protein may produce an autosomal dominant nephrogenic diabetes insipidus when the mutant aquaporin 2 protein associates with the wild-type normal protein to inhibit normal intracellular routing and function of the wild type.222

**Acquired Nephrogenic Diabetes Insipidus.** Producing a concentrated urine depends on maintaining hyperosmolality of the inner medulla of the kidney. Producing and maintaining hyperosmolality of the inner medulla requires that the kidney architecture be intact with an intact tubular structure of the loop of Henle, essential to the development of the countercurrent multiplier, and then a normal anatomy of the collecting duct to pass back through the inner medulla. The vascular structure must be anatomically intact so the hyperosmolality of the inner medulla is not washed away by normal blood flow. The broad definition of nephrogenic diabetes insipidus may include numerous chronic renal diseases that distort the architecture of the kidney. Vascular and anatomic causes of reduced concentration of urine are not considered here as diabetes insipidus because these are not disorders caused by abnormal function of vasopressin.224 Acquired nephrogenic diabetes insipidus associated with hypokalemia, hypercalcemia, and release of internal urinary tract obstruction are all associated with downregulation of aquaporin 2 and decreased function of vasopressin.220,221

Administration of lithium to treat psychiatric disorders is the most common cause of drug-induced acquired nephrogenic diabetes insipidus and illustrates the mechanisms.223 Lithium produces a decrease in urea transporters, reducing vasopressin-stimulated urea uptake and decreasing urea recycling, which reduces intermedullary osmolality.220,223 Even more dramatic is the reduction in aquaporin 2 levels to decrease water transport in the collecting duct.223 There is as much as a 95% decrease in aquaporin 2 content, and even the 5% of aquaporin 2 that persists is not normally transported to the renal principal cell membrane.226 The defect of aquaporins with lithium is slow to correct both in experimental animals and in humans and may be permanent.223,227 Demeclocycline is another drug commonly recognized to cause nephrogenic diabetes insipidus and is used clinically to treat SIADH (discussed later). See the review by Bendz and Aurell228 for a list of drugs that cause nephrogenic diabetes insipidus.

### Treatment of Nephrogenic Diabetes Insipidus

Adequate water intake should always be maintained and may be lifesaving in congenital nephrogenic diabetes insipidus. By definition these forms of diabetes insipidus do not respond to vasopressin or desmopressin, although there may rarely be some partial defects with some response to high doses of desmopressin.229,230 In congenital nephrogenic diabetes insipidus therapy is aimed at reducing symptomatic polyuria. This is done primarily by causing volume contraction with a low-sodium diet and a thiazide diuretic. The antidiuretic effect has been interpreted as due to contraction of ECF volume, decreased glomerular filtration rate, proximal sodium and water reabsorption, and decreased delivery of fluid to the collecting duct resulting in a decreased volume of urine.231 Studies have also demonstrated that thiazide diuretics may increase aquaporin 2 independent of vasopressin.232 All the thiazide diuretics appear to have similar effects. Potassium replacement or coadministration of a potassium-sparing antidiuretic may be desirable. There is an added effect obtained by coadministration of NSAIDs, but duodenal ulcer and gastrointestinal hemorrhage may be produced. Newer selective cyclooxygenase 2 inhibitors with less gastrointestinal effect have been reported to decrease water loss, but long-term safety has not been documented.233

Drug-induced nephrogenic diabetes insipidus should be treated by stopping the offending agent if possible. Persistence of nephrogenic diabetes insipidus can be treated by hydrochlorothiazide and amiloride. With the induced volume contraction, these patients should be closely followed for the development of renal or other toxicity of the drug that caused the diabetes insipidus.234 For example, volume contraction produced by thiazide diuretics when used to treat lithium-induced nephrogenic diabetes insipidus may decrease lithium excretion and predispose to lithium toxicity.228,234 The diuretic amiloride blocks Na+ channels in the luminal membrane of the collecting duct cells and inhibits lithium reabsorption, a unique advantage in treating lithium-induced nephrogenic diabetes insipidus.235 In animal studies of lithium-induced nephrogenic diabetes insipidus treatment with amiloride increased both the levels of aquaporin 2 and of urea transporters.225

Studies have reported the possibility of rescuing mutant receptors in nephrogenic diabetes insipidus. In autosomal dominant nephrogenic diabetes insipidus of type 2 the misfolded receptor protein is trapped in the quality control system of the endoplasmic reticulum. In some cases the defect may be transport rather than function, and were the receptor to reach the cell membrane, it would respond to vasopressin. V2 receptor antagonists (vaptans) have been reported as pharmacologic chaperones that combine with the misfolded receptor, changing the conformation to allow maturation and transport to the plasma membrane, where vasopressin (in excess of the vaptans) would cause the receptor to be activated.236-238 Similar studies of rescue have recently been reported with the nonpeptide V2 receptor agonists. These agonists combine with the mutant receptor trapped in the endoplasmic reticulum and allow the maturation of the mutant receptor. The rescued receptor is then inserted into the cell membrane and when stimulated by vasopressin or desmopressin generates sufficient cAMP to
move aquaporin 2 from the cytoplasm to the cell membrane to enhance water transport. Nonpeptide antagonists working as chaperones is a potential new treatment of nephrogenic diabetes insipidus, especially in patients with a partial disorder.

Sequencing of genes in all families with nephrogenic diabetes insipidus is recommended because of the small size of the genes to be sequenced and because of the value of the information. In X-linked disorders, carrier females can be distinguished from noncarrier females so it is known which sibling’s children are at risk and require special observation at birth. Molecular testing of newborns will confirm the need for long-term treatment to avoid complications in the affected children and obviate the need for dehydration or other testing in unaffected children.

Diabetes Insipidus in Association With Other Therapeutic Decisions

Routine Surgical Procedures

In all cases there should be preoperative consultation among the surgeon, the anesthesiologist, and the endocrinologist/nephrologist. For most routine surgical procedures the patient is not unconscious for a sufficiently long period to require anything more that administration of the usual dose of desmopressin and careful monitoring of fluids during the surgery to ensure overhydration. If the patient has been taking desmopressin orally but is now NPO (taking nothing by mouth), a parenteral dose can be administered before the procedure. If the procedure is especially long, one might consider a low-dose vasopressin given continuously with fluid as described earlier for postoperative or trauma-induced hypothalamic/neurohypophyseal diabetes insipidus. Close monitoring of serum sodium is essential. In nephrogenic diabetes insipidus there might be a greater emphasis on fluid replacement to avoid dehydration and hyponatremia.

Panhypopituitarism

Because hypothyroidism and adrenal insufficiency have a direct action on the kidney to inhibit the ability to excrete water, any patient who has anterior pituitary deficiency in association with diabetes insipidus is at risk to develop hyponatremia if treatment for diabetes insipidus is continued while treatment with thyroid hormone and (more dramatically) hydrocortisone is stopped. It is important that such patients maintain treatment of all anterior and posterior pituitary deficiencies continuously because the balance among these replacements is essential.

Promoting a Saline Diuresis

In certain clinical situations, such as chemotherapy or use of some contrast agents, diuresis is desirable to minimize renal toxicity. If desmopressin is continued and a large volume of normal saline is given, natriuresis and hyponatremia will be induced. Withholding desmopressin and replacing fluids with 5% dextrose in water (D5W) may lead to hyperglycemia, whereas replacing with normal saline may lead to hyponatremia. It has been reported that very low-dose vasopressin administered continuously intravenously (similar to that described earlier for comatose patients) can be used. In this case the dose of vasopressin is even lower (e.g., 0.08 to 0.1 mU/kg per hour) to allow a moderate and controlled diuresis. As with any situation in which vasopressin is given continuously, serum sodium must be checked regularly and the amount of fluids infused monitored carefully.

Hypertonic Encephalopathy

Hypertonic encephalopathy is uncommon in diabetes insipidus and is only seen when there is inadequate fluid intake in an adipsic patient or in a patient who is unconscious and not receiving adequate fluid supplementation. Conditions other than diabetes insipidus are the more common causes of hyponatremic encephalopathy. It may be caused by loss of hypotonic fluids by the kidney or the gut or by insensible losses or may be secondary to administration of hypertonic sodium-containing fluids or hyperalimentation. Sodium is mainly an extracellular electrolyte, and hyponatremia invariably leads to movement of water out of cells and cellular dehydration.

Studies indicate that in the brain so-called idiogenic osmoles are generated intracellularly, so the degree of cell shrinkage is less than would be expected based on the degree of hyponatremia. These idiogenic osmoles belong to three organic classes: polyols, trimethylamines, and amino acids and their derivatives. Loss of water from the brain occurs in minutes, and electrolytes enter the brain in a few hours, but the increase in organic osmoles occurs over several days. Similarly, when fluid is replaced, these intracellular organic osmoles decrease more slowly than the decrease in osmolality of ECF. This asynchrony increases the potential for cerebral edema and worsening of the neurologic condition with overzealous treatment of hyponatremia. In most cases of diabetes insipidus seen immediately after surgery or diagnosed promptly after head injury the diagnosis will be made within a few hours and therapy may be instituted promptly. In cases in which the duration of the hyponatremia is not known, the degree of correction of hyponatremia should not exceed 0.5 mEq/L per hour to prevent cerebral edema and convulsions.

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130 to 131 mEq/L, which represents a more appropriate level at which to define the occurrence of clinically significant cases of this disorder.\(^ {249} \) Even using these more stringent criteria, incidences from 7% to 53% have been reported in institutionalized geriatric patients.\(^ {250} \) Although hyponatremia and hypoosmolality are quite common, the majority of cases are relatively mild, and most are acquired during the course of hospitalization. Nonetheless, hyponatremia is important clinically because (1) severe hypoosmolality (serum \([\text{Na}^+] \) levels <120 mEq/L) is associated with substantial morbidity and mortality rates\(^ {251} \); (2) even relatively mild hypoosmolality can quickly progress to more dangerous levels during the course of therapeutic management of other disorders; (3) overly rapid correction of dangerous levels during the course of therapeutic management of other disorders; (3) overly rapid correction of hypoosmolality can itself cause severe neurologic morbidity and death\(^ {252} \); and (4) it has been observed that mortality rates are much higher, from 3-fold to 60-fold higher, in patients with even asymptomatic degrees of hypoosmolality compared to normonatremic patients.\(^ {253,254} \)

**Osmolality, Tonicity, and Serum Sodium Concentration**

As discussed previously, the osmolality of body fluid normally is maintained within narrow limits for each individual by osmotically regulated vasopressin secretion and thirst. Plasma osmolality can be determined directly by measuring the freezing-point depression or the vapor pressure of plasma. Alternatively, it can be calculated indirectly from the concentrations of the three major solutes in plasma:

\[
p\text{Osm} = 2([\text{Na}^+] + \text{(glucose/18)} + (\text{BUN/2.8})
\]

where plasma osmolality (pOsm) is measured in mOsm/kg H\(_2\)O, \([\text{Na}^+] \) in mEq/L, plasma glucose concentration in mg/dL, and blood urea nitrogen (BUN) in mg/dL. Direct measure and indirect calculation produce comparable results under most conditions. However, even though either of these methods will produce valid measures of total osmolality, this is not always equivalent to the effective osmolality, which is commonly referred to as the tonicity of the plasma. Only solutes such as \([\text{Na}^+]\) and \([\text{Cl}^-] \) that are impermeable to the cell membrane and remain relatively compartmentalized within the ECF space are effective solutes, because these solutes create osmotic gradients across cell membranes and regulate the osmotic movement of water between the intracellular fluid (ICF) compartment and the ECF compartment. Solutes that readily permeate cell membranes (e.g., urea, ethanol, methanol) are not effective solutes. Therefore, only the concentrations of effective solutes in plasma should be used to ascertain whether clinically significant hyperosmolality or hypoosmolality is present.

Sodium and its accompanying anions represent the major effective plasma solutes, so hyponatremia and hypoosmolality are usually synonymous. However, there are two situations in which hyponatremia will not reflect true hypoosmolality. The first is *pseudohyponatremia*, which is produced by marked elevations of either lipids or proteins in plasma. If serum \([\text{Na}^+] \) is measured by flame photometry, the concentration of sodium per liter of plasma is artifactualy decreased because of the larger relative proportion of plasma volume that is occupied by the excess lipids or proteins.\(^ {255} \) However, the increased protein or lipid will not appreciably change the total number of solute particles in solution, so the directly measured plasma osmolality will not be significantly affected. Measurement of serum \([\text{Na}^+] \) by ion-specific electrodes, which is now commonly employed by most clinical laboratories, is less influenced by high concentrations of lipids or proteins than is measurement of serum \([\text{Na}^+] \) by flame photometry. However, this can still occur if the electrode measurement is done using a diluted sample of the serum.

The second situation in which hyponatremia does not reflect true plasma hypoosmolality occurs when high concentrations of effective solutes other than \([\text{Na}^+] \) are present in the plasma. The initial hyperosmolality produced by the additional solute causes an osmotic shift of water from the ICF to the ECF, which in turn produces a dilutional decrease in serum \([\text{Na}^+] \). Once equilibrium between both fluid compartments is achieved, the total effective osmolality remains relatively unchanged. This situation most commonly occurs with hyperglycemia and represents a frequent cause of hyponatremia in hospitalized patients, accounting for up to 10% to 20% of all cases.\(^ {253} \) Misdiagnosis of true hypoosmolality in such cases can be avoided by measuring plasma osmolality directly or, alternatively, by correcting the measured serum \([\text{Na}^+] \) for the glucose elevation. Traditionally, this correction factor has been 1.6 mEq/L for each 100-mg/dL increase in serum glucose concentration above normal levels,\(^ {256} \) but some studies have shown a more complex relation between hyperglycemia and serum \([\text{Na}^+] \) and reported that a more accurate correction factor is closer to 2.4 mEq/L.\(^ {257} \) When the plasma contains significant amounts of unmeasured solutes, such as osmotic diuretics, radiographic contrast agents, and some toxins (ethanol, methanol, and ethylene glycol), plasma osmolality cannot be calculated accurately, and in these situations osmolality must be ascertained by direct measurement.

**Pathogenesis of Hypoosmolality**

Water moves freely between the ICF and ECF, and consequently, osmolality will always be equivalent in both of these fluid compartments. Because the bulk of body solute comprises electrolytes, namely, the exchangeable \([\text{Na}^+] \) in the ECF and the exchangeable \([\text{K}^+] \) in the ICF, along with their associated anions, total body osmolality (Osm\(_{TB}\)) will largely be a function of these parameters:\(^ {258} \)

\[
\text{Osm}_{TB} = \text{Osm}_{ECF} = \text{Osm}_{ICF}
\]

\[
\text{Osm}_{ECF} = (\text{ECF solute} + \text{ICF solute})/\text{body water}
\]

According to this definition, the presence of plasma hypoosmolality indicates a relative excess of water to solute in the ECF. This can be produced either by an excess of body water, resulting in a *dilution* of remaining body solute, or by a *depletion* of body solute, either \([\text{Na}^+]\) or \([\text{K}^+]\), relative to body water. This classification is an oversimplification, because most hypoosmolar states involve significant components of both solute depletion and water retention. Nonetheless, it is conceptually useful for understanding the mechanisms underlying the pathogenesis of hypoosmolality and as a framework for therapy of hypoosmolar disorders.

**Solute Depletion.** Depletion of body solute can result from any significant losses of ECF. Body fluid losses by themselves rarely cause hypoosmolality because excreted or secreted body fluids are usually isotonic or hypotonic relative to plasma and therefore tend to increase plasma osmolality. When hypoosmolality accompanies ECF losses, it is the result of replacement of body fluid losses by more hypotonic solutions either by drinking or by infusion, thereby diluting the remaining body solutes. If the solute losses are marked, these patients show signs of volume depletion (e.g., addisonian crisis). However, such patients often have a more deceptive clinical presentation because
the volume deficits have been partially replaced. Moreover, they may not manifest signs or symptoms of cellular dehydration because osmotic gradients will draw water into the ICF, which is relatively hypertonic to the solute-depleted ECF. Therefore, clinical evidence of hypovolemia strongly supports solute depletion as the cause of plasma hypoosmolality, but absence of clinically evident hypovolemia never completely eliminates this as a possibility. Although ECF solute losses are responsible for most cases of depletion-induced hypoosmolality, ICF solute loss can also cause hypoosmolality as a result of osmotic water shifts from the ICF to the ECF. This mechanism contributes to some cases of diuretic-induced hypoosmolality in which depletion of total body K+ often occurs.269

**Water Retention.** Despite the importance of solute depletion in some patients, most cases of clinically significant hypoosmolality are caused by increases in total body water rather than by primary losses of extracellular solute. This can occur because of either impaired renal free water excretion or excessive free water intake. The former accounts for most hypoosmolar disorders because normal kidneys have sufficient diluting capacity to allow excretion of 18 to 24 L/day of free water. Intakes of this magnitude are occasionally seen in some psychiatric patients but not in most patients with SIADH in whom fluid intake averages 2 to 3 L/day.260 Consequently, dilutional hypoosmolality usually is the result of an abnormality of renal free water excretion. The renal mechanisms responsible for impairments in free water excretion can be subgrouped according to whether the major impairment in free water excretion occurs in proximal or distal parts of the nephron, or both. Any disorder that leads to a decrease in glomerular filtration rate causes increased reabsorption of both Na+ and water in the proximal tubule. As a result, the ability to excrete free water is limited because of decreased delivery of tubular fluid to the distal nephron. Disorders that cause a decreased glomerular filtration rate in the absence of significant ECF fluid losses are, for the most part, edema-forming states associated with decreased effective arterial blood volume (EABV) and secondary hyperaldosteronism.261 Even though these conditions are characterized by increased proximal reabsorption of both Na+ and fluid, water retention also results from increased distal reabsorption caused by nonsomatic baroreceptor-mediated stimulated increases in plasma vasopressin levels. Distal nephron impairments in free water excretion are characterized by an inability to dilute tubular fluid maximally. These disorders are usually associated with abnormalities in the secretion of vasopressin. Just as depletion-induced hypoosmolar disorders usually include an important component of secondary impairments of free water excretion, most dilutional-induced hypoosmolar disorders also involve significant degrees of secondary solute depletion. This is described later with SIADH.

Some dilutional disorders do not fit well into either category, specifically the hyponatremia that sometimes occurs in patients who ingest large volumes of beer with little food intake for prolonged periods (beer potomania).262 Even though the volume of fluid ingested may not seem sufficiently excessive to overwhelm renal diluting mechanisms, free water excretion is limited by very low urinary solute excretion, thereby causing water retention and dilutional hyponatremia.

**Adaptation to Hyponatremia: ICF and ECF**

**Volume Regulation**

Many past studies have suggested that the combined effects of water retention plus urinary solute excretion cannot adequately explain the degree of plasma hypoosmolality observed in patients.246,263 This observation led to the theory of cellular inactivation of solute, which suggested that as ECF osmolality falls, water moves into cells along osmotic gradients, thereby causing the cells to swell; at some point during this volume expansion, the cells theoretically osmotically inactivate some of their intracellular solutes as a defense mechanism to prevent continued cellular swelling with subsequent detrimental effects on cell function and survival. This effect would decrease the intracellular osmolality, allowing water to shift back out of the ICF into the ECF, thereby further worsening the dilution-induced hypoosmolality. Despite the appeal of this theory, its validity has never been demonstrated conclusively in either human or animal studies. An alternative theory is that cell volume is maintained under hypoosmolar conditions by extrusion of intracellular solutes such as potassium.264 Whole brain volume regulation via electrolyte losses was first described by Yannet,265 and has long been recognized as the mechanism by which the brain is able to adapt to hyponatremia and limit brain edema to sublethal levels.266 Following the recognition that low-molecular-weight organic compounds, called organic osmolytes, also constituted a significant osmotic component of a wide variety of cells, studies demonstrated the accumulation of these compounds in response to hyperosmolality in both kidney267 and brain268 tissue and conversely that the brain also loses organic osmolytes in addition to electrolytes during volume regulation to hypoosmolar conditions in experimental animals269,270 and human patients.271 These losses occur relatively quickly (within 24 to 48 hours in rats) and can account for as much as one third of the brain solute losses during hyponatremia.272 Such coordinate losses of both electrolytes and organic osmolytes from brain cells allow effective regulation of brain volume during chronic hyponatremia.

Although recent studies of volume regulation during hyponatremia have focused on the brain, all cells regulate volume by cellular losses of both electrolyte and organic solutes to varying degrees. However, volume regulatory processes are not limited to cells. In most cases of hyponatremia induced by stimulated antiuricuresis and water retention, natriuresis also regulates the volumes of the ECF and intravascular spaces. Both experimental and clinical observations are consistent with ECF volume regulation via secondary solute losses. First, the concentrations of most blood constituents other than Na+ and CI− are not decreased in patients with SIADH,273 suggesting that plasma volume is not nearly as expanded as would be predicted simply by the measured decreases in serum [Na+]. Second, an increased incidence of hypertension has never been observed in patients with SIADH, again evidence against significant expansion of the arterial blood volume. Third, results of animal studies in both dogs274 and rats275 have indicated that a significant component of chronic hyponatremia is attributable to secondary Na+ losses rather than water retention; the relative contributions from water retention versus sodium loss vary with the duration and severity of the hyponatremia: water retention was found to be the major cause of decreased serum [Na+] in the first 24 hours of induced hyponatremia in rats, but Na+ depletion then became the predominant etiologic factor after longer periods (7-14 days) of sustained hyponatremia, particularly at very low (<115 mEq/L) serum [Na+] levels.275 Finally, multiple studies of body fluid compartment volumes in hyponatremic patients have not demonstrated either plasma or ECF expansion. For example, a report of body fluid space measurements using isotope dilution techniques in hyponatremic and normonatremic patients with
many different hypoosmolality, and therapy. Curr Opin Nephrol Hypertens. 1993;2:626-652.)

Figure 10-5 Schematic illustration of potential changes in whole-body fluid compartment volumes at various times during adaptation to hyponatremia. A, Under basal conditions, the concentrations of effective solutes in the extracellular fluid ([S]ECF) and in the intracellular fluid ([S]ICF) are in osmotic balance. B, During the initial phase of water retention resulting from inappropriate antidiuresis, the excess water distributes across total body water, causing expansion of both ECF and ICF volumes (dotted lines), with equivalent dilutional decreases in both [S]ICF and [S]ECF. C, In response to the volume expansion, compensatory volume regulatory decreases (VRD) occur to reduce the effective solute content of the ECF (via pressure diuresis and natriuretic factors) and the ICF (via increased electrolyte and osmolyte extrusion mediated by stretch-activated channels and downregulation of synthesis of osmolytes and osmolyte uptake transporters). D and E, If both processes go to completion, such as under conditions of fluid restriction, a final steady state can be reached in which ICF and ECF volumes have returned to normal levels but [S]ICF and [S]ECF remain low. In most cases, this final steady state is not reached, and moderate degrees of ECF and ICF expansion persist, although they are significantly less than would be predicted from the decrease in body osmolality (D). Consequently, the degree to which hyponatremia is the result of dilution due to water retention versus solute depletion from volume regulatory processes can vary markedly, depending on which phase of adaptation the patient is in and the relative rates at which the different compensatory processes occur. For example, delayed ICF VRD can worsen hyponatremia because of shifts of intracellular water into the ECF as intracellular organic osmolytes are extruded and subsequently metabolized; this likely accounts for some component of the hyponatremia that was unexplained by the combination of water retention and sodium excretion in early clinical studies. (From Verbalis JG: Hyponatremia: epidemiology, pathophysiology, and therapy. Curr Opin Nephrol Hypertens. 1993;2:626-652.)

small cell lung carcinoma showed no differences between the two groups with regard to exchangeable sodium space, ECF volume by $^{35}$SO$_4$ distribution, or total body water.276 Figure 10-5 schematically illustrates the volume regulatory processes that occur in response to water retention induced by inappropriate antidiuresis.

Differential Diagnosis of Hyponatremia and Hypoosmolality
Because of the multiplicity of disorders causing hypoosmolality and the fact that many involve more than one pathologic mechanism, a definitive diagnosis is not always possible at the time of initial presentation. Nonetheless, an approach based on clinical parameters of ECF volume status and urine sodium concentration generally allows a sufficient categorization for appropriate decisions regarding initial therapy and further evaluation.

Decreased Extracellular Fluid Volume. Clinically detectable hypovolemia always signifies total body solute depletion. A low urine [Na+] indicates a nonrenal cause and an appropriate renal response. A high urine [Na+] indicates that renal causes of solute depletion are more likely. Therapy with thiazide diuretics is the most common cause of renal solute losses,259 particularly in the elderly,277 but mineralocorticoid deficiency as a result of adrenal insufficiency or mineralocorticoid resistance must be considered as well as (less commonly) renal solute losses due to salt-wasting nephropathy (e.g., polycystic kidney disease, interstitial nephritis, or chemotherapy).

Increased Extracellular Fluid Volume. Clinically detectable hypervolemia always signifies total body Na+ excess. In these patients hypoosmolality results from an even greater expansion of total body water caused by a marked reduction in the rate of water excretion (and sometimes an increased rate of water ingestion). The impairment in water excretion is secondary to a decreased EABV,261 which increases the reabsorption of glomerular filtrate not only in the proximal nephron but also in the distal and collecting tubules by stimulated secretion of vasopressin. These patients generally have a low urine [Na+] because of secondary hyperaldosteronism. However, under certain conditions urine [Na+] may be elevated if there is concurrent diuretic therapy or a solute diuresis (e.g., glucosuria in diabetics) or after successful treatment of the underlying disease (e.g., improved cardiac output in patients with congestive heart failure).

Normal Extracellular Fluid Volume. Many different hypoosmolar disorders present with euvolemia, and measurement of urinary [Na+] is an especially important first step in their assessment.278 A high urine [Na+] usually implies a distally mediated, dilution-induced hypoosmolality such as SIADH. However, glucocorticoid deficiency can mimic SIADH so closely that these two disorders are often indistinguishable in terms of water balance. Hyponatremia from diuretic use also can present without clinically evident hypovolemia, and the urine [Na+] will usually be elevated.259 A low urine [Na+] suggests a depletion-induced hypoosmolality from ECF losses with subsequent volume replacement by water or other hypotonic fluids. The solute loss often is nonrenal, but an important exception is recent cessation of diuretic therapy, because urine [Na+] can decrease to low values within 12 to 24 hours after discontinuation of the drug. A low urine [Na+] also can also be seen during the recovery phase from SIADH.

Clinical Aspects of SIADH
SIADH is the most common cause of euvolemic hypoosmolality as well as the single most common cause of all types of hypoosmolality encountered in clinical practice, with prevalence rates from 20% to 40% among all hypoosmolar patients.253,260 The clinical criteria necessary to diagnose SIADH remain basically those set forth by Bartter and Schwartz in 1967:246

1. Decreased effective osmolality of the ECF (plasma osmolality <275 mOsm/kg H$_2$O). Pseudohyponatremia or hyperglycemia alone must be excluded.
2. Inappropriate urinary concentration at some level of hypoosmolality. This does not mean that urine osmolality must be greater than plasma osmolality, only that it
is less than maximally dilute (i.e., urine osmolality >100 mOsm/kg H₂O). Also, urine osmolality need not be elevated inappropriately at all levels of plasma osmolality, because in the reset osmostat variant form of SIADH, vasopressin secretion can be suppressed with resultant maximal urinary dilution if plasma osmolality is decreased to sufficiently low levels.²⁷⁹

3. Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites). Hypovolemia and hypervolemia strongly suggest different causes of hypoosmolality. Patients with SIADH can become hypovolemic or hypervolemic for other reasons, but in such cases it is impossible to diagnose the underlying inappropriate antidiuresis until the patient is rendered euvolemic and is found to have persistent hypoosmolality.

4. Elevated urinary sodium excretion with normal salt and water intake. This criterion is included because of its utility in differentiating between hypoosmolality caused by a decreased EABV, in which case renal Na⁺ conservation occurs, and distal dilution-induced disorders, in which urine Na⁺ excretion is normal or increased secondary to ECF volume expansion. Patients with SIADH can have low urine Na⁺ excretion if they subsequently become hypovolemic or solute depletes, conditions that sometimes follow severe salt and water restriction. Consequently, a high urine Na⁺ excretion is the rule in most patients with SIADH; thus, its presence does not guarantee this diagnosis, and its absence does not rule out the diagnosis.

5. Absence of other potential causes of euvolemic hypoosmolality, notably, hypothyroidism, hypocortisolism (Addison disease or pituitary ACTH insufficiency), and diuretic use.

Several other criteria support, but are not essential for, a diagnosis of SIADH. Volume expansion and vasopressin acting on V₁ receptors in the kidney increase the clearance of uric acid, so hypouricemia is found with SIADH. When patients are hyponatremic, values of uric acid are reported to be lower than 4 mg/dL (<0.24 mmol/L).²⁸⁰ A water-loading test is of value when there is uncertainty regarding the cause of modest degrees of hypoosmolality in euvolemic patients, but it does not add useful information if the plasma osmolality is already lower than 275 mOsm/kg H₂O. Inability to excrete a standard water load normally (with normal excretion defined as a cumulative urine output of at least 90% of the administered water load within 4 hours and suppression of urine osmolality to <100 mOsm/kg H₂O) confirms the presence of an underlying defect in free water excretion. However, water excretion is abnormal in almost all disorders that cause hypoosmolality, whether dilutional or depletion-induced with secondary impairments in free water excretion. Two exceptions are primary polydipsia, in which hypoosmolality can rarely be secondary to excessive water intake alone, and the reset osmostat variant of SIADH, in which normal excretion of a water load can occur once plasma osmolality falls below the new set-point for vasopressin secretion.

Another supportive criterion is an inappropriately elevated plasma vasopressin level in relation to plasma osmolality. However, several factors limit the utility of vasopressin measurements to diagnose SIADH. First, although plasma vasopressin levels are elevated in most patients with this syndrome, the elevations generally remain within the normal physiologic range and are abnormal only in relation to plasma osmolality (Fig. 10-6). Second, 10% to 20% of patients with SIADH do not have measurably elevated plasma vasopressin levels and are at the limits of detection by radioimmunoassay (see Fig. 10-6).²⁸¹ Third (and perhaps most important), most disorders causing solute and volume depletion or decreased EABV are associated with elevations of plasma vasopressin levels secondary to nonosmotic hemodynamic stimuli.

Etiology

Although the list of disorders associated with SIADH is long (Table 10-3), they can be divided into several major etiologic groups, including tumors, CNS disorders, drugs, and pulmonary disorders.

Tumors. The most common association of SIADH is with tumors. Many different types of tumors have been associated with SIADH, but bronchogenic carcinoma of the lung has been uniquely associated with SIADH since the first description of this disorder in 1957.²⁴⁵ In virtually all cases, the bronchogenic carcinomas causing this syndrome have been of the small cell variety. The incidence of hyponatremia is reported to be as high as 11% among all patients with small cell carcinoma²⁵² and as high as 33% among those with more extensive disease.²⁵³ The high incidence of small cell carcinoma of the lung makes it imperative that all adult patients presenting with an otherwise unexplained SIADH be investigated thoroughly and aggressively for a possible lung tumor. Head and neck cancers account for another group of malignancies associated with relatively higher incidences of SIADH,²⁴⁴ and some of these tumors have clearly been shown to synthesize vasopressin.²⁸⁵ A report from a large cancer hospital showed an incidence of hyponatremia for all malignancies of 3.7%, with approximately one third of these due to SIADH.²⁸⁶

Central Nervous System Disorders. A large number of different CNS disorders have been associated with SIADH, but there has been no common denominator linking them. This is not surprising when one considers the neuroanatomy described earlier. Magnocellular vasopressin neurons receive excitatory inputs from osmoreceptive cells located in the anterior hypothalamus, but also a major innervation from brainstem cardiovascular regulatory and emetic centers. Although various components of these pathways

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**Figure 10-6** Plasma arginine vasopressin (AVP) levels in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a function of plasma osmolality. Each point depicts one patient at a single point in time. The shaded area represents AVP levels in normal subjects over physiologic ranges of plasma osmolality. The lowest measurable plasma AVP level that could be detected with this radioimmunoassay was 0.5 pg/mL. (From Robertson GL, Aycinena P, Zerbe RL. Neuropathic disorders of osmoregulation. Am J Med. 1982;2:339-353.)
TABLE 10-3

Common Causes of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

<table>
<thead>
<tr>
<th>Tumors</th>
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<tbody>
<tr>
<td>Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)</td>
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<td></td>
</tr>
<tr>
<td>Nonchest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)</td>
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Central Nervous System Disorders

| Mass lesions (tumors, brain abscesses, subdural hematoma) | | |
| Inflammatory diseases (encephalitis, meningitis, systemic lupus erythematosus, acute intermittent porphyria, multiple sclerosis) | | |
| Degenerative/demyelinating diseases (Guillain-Barré syndrome, spinal cord lesions) | | |
| Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transsphenoidal adenectomy, hydrocephalus) | | |

Drug-Related

| Stimulated release of AVP (nicotine, phenothiazines, tricyclics) | | |
| Direct renal effects or potentiation of AVP antidiuretic effects (dDAVP, oxytocin, prostaglandin synthesis inhibitors) | | |
| Mixed or uncertain actions (ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxyamphetamine [ecstasy], omeprazole; serotonin reuptake inhibitors, vincristine) | | |

Pulmonary

| Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema) | | |
| Mechanical/ventilatory causes (acute respiratory failure, COPD, positive-pressure ventilation) | | |

Other Causes

| Acquired immunodeficiency syndrome (AIDS) and AIDS-related complex | | |
| Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking) | | |
| Senile atrophy | | |
| Idiopathic | | |

ACE, angiotensin-converting enzyme; AVP, arginine vasopressin; COPD, chronic obstructive pulmonary disease; dDAVP, desmopressin.

have yet to be elucidated fully, many of them appear to have inhibitory as well as excitatory components. Consequently, any diffuse CNS disorder can potentially cause vasopressin hypersecretion either by nonspecificly exciting these pathways via irritative foci or, alternatively, by disrupting them and thereby decreasing the level of inhibition.

Drugs. Drug-induced hyponatremia is a common cause of hypoosmolality. Table 10-3 lists some of the agents that have been associated with SIADH, but new drugs are added continually. Pharmacologic agents may stimulate secretion of vasopressin, activate renal V2 receptors, or potentiate the antidiuretic effect of vasopressin. Not all of the drug effects are fully understood, and many appear to work through a combination of mechanisms. A particularly interesting, and clinically important, class of agents is the selective serotonin reuptake inhibitors (SSRIs). Hyponatremia following SSR1 administration has been reported almost exclusively in the elderly, with rates as high as 22% to 28%, although in larger series the incidence was closer to 1 in 200. A similar effect is likely also responsible for the recent reports of severe fatal hyponatremia caused by use of the recreational drug 3,4-methylenedioxyamphetamine (MDMA, ecstasy), which possesses substantial serotoninergic activity.

Pulmonary Disorders. A variety of pulmonary disorders have been associated with this syndrome, but other than tuberculosis, acute pneumonia, and advanced chronic obstructive lung disease, the occurrence of hypoosmolality has been noted only sporadically. Hypoxia stimulates secretion of vasopressin in animals, but in humans hypercarbia is more associated with abnormal water retention. Elevated vasopressin may be limited to the initial days of hospitalization, when respiratory failure is most marked. Therefore, with SIADH in nontumor pulmonary disease the pulmonary disease is obvious with severe dyspnea or extensive radiographically evident infiltrates and the inappropriate antidiuresis will usually be limited to the period of respiratory failure. Mechanical ventilation can cause SIADH via inappropriate secretion of vasopressin via decreased venous return.

Other Causes. In acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) and in patients with HIV infection, incidence of hyponatremia has been reported to be as high as 30% to 38% in adults and children. Although there are many potential causes, including dehydration, adrenal insufficiency, and pneumonitis, from 12% to 68% of AIDS patients who develop hyponatremia appear to meet criteria for a diagnosis of SIADH.

Not unexpectedly, some of the medications used to treat these patients may cause the hyponatremia, either via direct renal tubular toxicity or induced SIADH.

Elderly patients often develop SIADH without any apparent underlying cause, and the high incidence of hyponatremia in geriatric patients suggests that the normal aging process may be accompanied by abnormalities of regulation of water balance and of secretion of vasopressin, as noted earlier. Such an effect could potentially account for the fact that drug-induced hyponatremia occurs much more frequently in elderly patients. In a series of 50 consecutive elderly patients meeting criteria for SIADH, 60% remained idiopathic despite rigorous evaluation, leading the authors to conclude that extensive diagnostic procedures were not warranted in such elderly patients if routine history, physical examination, and laboratory evaluation failed to suggest an underlying cause.

Pathophysiology

Sources of Vasopressin Secretion. Elevated plasma levels of vasopressin can be broadly divided into those associated with paraneoplastic (ectopic) secretion of vasopressin or pituitary hypersecretion of vasopressin. There is substantial cumulative evidence that tumor tissue can, in fact, synthesize vasopressin, but it is not certain that all tumors associated with SIADH do so, because only about half of small cell carcinomas have been found to contain vasopressin immunoreactivity, and many of the tumors listed in Table 10-3 have not been carefully studied.

Pituitary Vasopressin Secretion: Inappropriate Versus Appropriate. In the majority of cases of SIADH, the vasopressin secretion originates from the posterior pituitary. This is also true of more than 90% of all cases of hyponatremia, including patients with hypovolemic and hypervolemic hyponatremia. This raises the question of what constitutes inappropriate secretion of vasopressin. Secretion of vasopressin in response to a hypovolemic stimulus is clearly physiologically appropriate, but when it leads to symptomatic hyponatremia it could be considered inappropriate for the ECF osmolality. Despite these semantic conundrums, the diagnosis of SIADH should be based on the original Schwartz-Bartter criteria and specifically exclude other clinical conditions that cause known impairments in free water excretion even when these are mediated by a...
Secondary nonosmotic physiologic stimulation of vasopressin secretion. Without maintaining these distinctions, arguably as some may be, the definition of SIADH becomes too broad to retain any practical clinical utility.

Patterns of Vasopressin Secretion. Studies of plasma vasopressin levels in patients with SIADH during graded increases in plasma osmolality produced by hypertonic saline administration have defined four patterns of secretion (Fig. 10-7): (1) random hypersecretion of vasopressin; (2) inappropriate nonsuppressible basal vasopressin release but normal secretion in response to osmolar changes above basal plasma osmolality; (3) a reset osmostat system, whereby vasopressin is secreted at an abnormally low threshold of plasma osmolality but otherwise displays a normal response to relative changes in osmolality; and (4) low or even undetectable plasma vasopressin levels despite classic clinical characteristics of SIADH. The first pattern, unregulated vasopressin secretion, is often observed in patients exhibiting paraneoplastic vasopressin production. Resetting of the osmotic threshold for vasopressin secretion has been well described with volume depletion and edema-forming states with EABV, but most patients with a reset osmostat are clinically euvolemic and may represent SIADH. The best physiologic example of a reset osmostat occurs in pregnancy, as discussed earlier. Perhaps the most perplexing aspect of the reset osmostat pattern is its occurrence in patients with tumors, which suggests that in some of these cases a tumor-related mechanism may affect pituitary vasopressin secretion. The pattern of SIADH that occurs without measurable vasopressin secretion is not yet well understood, but the positive response of one such patient to a vasopressin V2-receptor antagonist would suggest that this may represent increased renal sensitivity to low circulating levels of vasopressin. Recent studies of pediatric patients with hyponatremia and measurable plasma vasopressin levels led to the discovery of an activating mutation of the vasopressin V2 receptor as the cause of their inappropriate antidiuresis. It is more appropriate to call these cases the nephrogenic syndrome of inappropriate antidiuresis, reserving SIADH only for those cases in which measured plasma vasopressin levels are really inappropriate. Although the incidence of nephrogenic syndrome of inappropriate antidiuresis in the general population is unknown, the description of Belgian kindred with this mutation suggests that it can present later in life as well as in childhood. It is surprising that no correlation has been found between any of these patterns of secretion of vasopressin and the various causes of SIADH.

Contribution of Natriuresis to the Hyponatremia of SIADH. Since the original cases studied by Schwartz and Bartter, increased renal Na+ excretion has been one of the cardinal manifestations of SIADH, indeed one which later became embedded in the requirements for its diagnosis. Demonstration that the natriuresis accompanying administration of antidiuretic hormone is not due to vasopressin itself but rather to the volume expansion produced as a result of water retention was unequivocally shown by Leaf and coworkers even before the description of the disorder. Although a negative Na+ balance occurs during the development of hyponatremia in patients with SIADH, eventually urinary sodium excretion simply reflects daily sodium intake. Thus, the term renal sodium wasting is used to describe continued excretion of sodium despite being hyponatremic, but in reality there is a new steady state in which patients are in neutral sodium balance. Studies of long-term antidiuretic-induced hyponatremia in both dogs and rats have indicated that a large proportion of the hyponatremia was attributable to secondary Na+ losses rather than to water retention, but the natriuresis did not actually worsen the hyponatremia; rather, it allowed volume regulation of ECF. Secondary natriuresis in patients with SIADH likely explains the failure to find expanded plasma or ECF volumes using tracer dilution techniques (see Fig. 10-S).

Cerebral Salt Wasting. The degree to which hyponatremia might occur primarily as a result of primary natriuresis is controversial. Cerebral salt-wasting syndrome (CSWS) was proposed by Peters and colleagues in 1950 as an explanation for the natriuresis and hyponatremia that sometimes accompany intracranial disease, particularly subarachnoid hemorrhage, in which up to one third of patients often develop hyponatremia. After the description of SIADH in 1957, such patients were generally assumed to have hyponatremia secondary to vasopressin hypersecretion with a secondary natriuresis. However, over the past decade clinical and experimental data have been interpreted to indicate that some patients with subarachnoid hemorrhage and other intracranial diseases indeed have a primary natriuresis leading to volume contraction rather than SIADH, and the elevated plasma vasopressin levels may be physiologically appropriate for the degree of volume contraction. With regard to the potential mechanisms of natriuresis, both plasma and CSF levels of atrial natriuretic peptide are elevated in many patients with subarachnoid hemorrhage and have been found to correlate variably with hyponatremia in patients with intracranial diseases. However, clearly documented SIADH also is frequently associated with elevated plasma levels of atrial natriuretic peptide, so this finding does not prove causality. In other disorders of hyponatremia due to Na+ wasting (e.g., Addison disease) and diuretic-induced hyponatremia, infusion of saline restores normal ECF volume and plasma toxicity by shutting off the secondary vasopressin secretion. In subarachnoid hemorrhage, however, large volumes of isotonic saline sufficient to maintain plasma volume did not change the incidence of hyponatremia.
Those authors who have distinguished CSWS from SIADH have emphasized that in CSWS the primary disorder, salt wasting, produces convincing evidence of decreased ECF volume. There are only a few case reports of patients after traumatic brain injury or neurosurgery who while being observed in the hospital have acute onset of massive diuresis and natriuresis with clear evidence of volume contraction by weight loss, decreased central venous pressure, increased blood urea nitrogen, or increased hematocrit. Most of these cases have been in children and have responded to replacement with normal or hypertonic saline, but concurrent treatment with fludrocortisone has also been advocated. However, a recent study of 100 consecutive adult patients with acute nontraumatic aneurysmal subarachnoid hemorrhage found that the cause of the hyponatremia was attributable to SIADH in 71.4% and acute glucocorticoid deficiency in 8.2%, with the remaining cases caused by incorrect intravenous fluid administration or hypovolemia. Most significantly, no cases were found that met historically accepted criteria for a diagnosis of CSWS. This suggests that CSWS is an exceedingly rare cause of hyponatremia with intracranial disorders.

Renal Escape From Antidiuresis. In addition to excreting osmoles to bring volumes back toward normal, there are intrarenal adaptations that allow excretion of more water. Chronic stimulation by vasopressin in SIADH produces dramatic increases of aquaporin 2 content and insertion into the collecting duct principal cell membranes, which increases the efficiency of water retention and aggravates the disease. However, the induced volume expansion and hypotonicity act on the tubular cells of the collecting duct to decrease the content and action of aquaporin 2 substantially, thus decreasing the amount of water resorbed in spite of high vasopressin levels. Experimental studies have suggested that this effect may be due to downregulation of vasopressin V2 receptor expression in the kidney. This renal “escape” therefore represents another (in addition to natriuresis) adaptation that allows patients with persistent SIADH to come into a new steady state of Na+ and water balance despite low serum sodium concentrations.

Clinical Manifestations of Hypoosmolar Disorders

Regardless of the cause of hypoosmolality, most clinical manifestations are similar. Non-neurologic symptoms are relatively uncommon, although a number of cases of rhabdomyolysis have been reported, presumably secondary to osmotically induced swelling of muscle fibers. Hypoosmolality is primarily associated with a broad spectrum of neurologic manifestations, ranging from mild nonspecific symptoms (e.g., headache, nausea) to more significant disorders (e.g., disorientation, confusion, obtundation, focal neurologic deficits, and seizures). This neurologic symptom complex has been termed hyponatremic encephalopathy and primarily reflects brain edema resulting from osmotic water shifts into the brain because of decreased effective plasma osmolality. Significant neurologic symptoms generally do not occur until serum [Na+] falls below 125 mmol/L and the severity of symptoms are roughly correlated with the degree of hypoosmolality. However, individual variability is marked, and for any single patient, the level of serum [Na+] at which symptoms appear cannot be predicted.

The rate of fall of serum [Na+] is often more strongly correlated with morbidity and mortality than is the actual magnitude of the decrease. The reason is that the volume-adaptation process takes a finite period of time to complete, and the more rapid the fall in serum [Na+], the more brain edema will be accumulated before the brain is able to volume-regulate. Thus, there is a much higher incidence of neurologic symptoms, as well as a higher mortality rate, in patients with acute hyponatremia than in those with chronic hyponatremia. For example, the most dramatic cases of death due to hyponatremic encephalopathy have generally been reported in postoperative patients in whom hyponatremia develops rapidly as a result of intravenous infusion of hypotonic fluids. In such cases nausea and vomiting are frequently overlooked as potential early signs of increased intracranial pressure. Critically ill patients with unexplained seizures also should be immediately evaluated for possible hyponatremia, because as many as one third of such patients have a serum [Na+] lower than 125 mEq/L as the cause of the seizure activity. Underlying neurologic disease and non-neurologic metabolic disorders (e.g., hypoxia, acidosis, hypercalcemia) can raise the level of plasma osmolality at which CNS symptoms occur.

In the most severe cases of hyponatremic encephalopathy, death results from respiratory failure after tentorial cerebral herniation and brainstem compression. One quarter of patients with severe postoperative hyponatremic encephalopathy manifested hypercapnic respiratory failure, the expected result of brainstem compression; but three quarters of these patients had pulmonary edema as the apparent cause of the hypoxia. Studies of acute hyponatremia after marathon races have shown hypoxia and pulmonary edema in association with brain edema. These results suggest the possibility that hypoxia from noncardiogenic pulmonary edema may represent an early sign of developing cerebral edema even before brainstem compression and tentorial herniation. Clinical studies have suggested that menstruating women and young children may be particularly susceptible to the development of neurologic morbidity and death during hyponatremia, especially in the acute postoperative setting. However, other studies have failed to corroborate these findings.

Once the brain has volume-regulated via solute losses, thereby reducing brain edema, neurologic symptoms are not as prominent and may even be virtually absent. This accounts for the fairly common finding of relatively asymptomatic patients even with severe levels of hyponatremia. Despite this powerful adaptation process, chronic hyponatremia is frequently associated with neurocognitive symptoms, albeit milder and subtler in nature, such as headaches, nausea, mood disturbances, depression, difficulty concentrating, slowed reaction times, unstable gait, increased falls, confusion, and disorientation. Even in patients adjudged to be asymptomatic by virtue of a normal neurologic examination, accumulating evidence suggests that there may be previously unrecognized adverse effects as a result of chronic hyponatremia, including gait instability and increased falls. The clinical significance of the data on increased gait instability and falls in hyponatremic patients would be an increased fracture rate, which has now been documented in multiple international retrospective studies. More recently published studies have shown that hyponatremia is also associated with increased bone loss in experimental animals and a significant increased odds ratio for osteoporosis of the femoral neck in humans over the age of 50 in the National Health and Nutrition Examination Survey (NHANES) III database. Thus, the major clinical significance of chronic hyponatremia may lie in the increased morbidity and mortality rates associated with falls and fractures in the elderly population.
Therapy of SIADH and Other Hypoosmolar Disorders

General Principles

Correction of hyponatremia is associated with markedly improved neurologic outcomes in patients with severely symptomatic hyponatremia. In a retrospective review of patients who presented with severe neurologic symptoms and serum [Na+] lower than 125 mmol/L, prompt therapy with isotonic or hypertonic saline resulted in a correction in the range of 20 mEq/L over several days and neurologic recovery in almost all cases; in contrast, in patients who were treated with fluid restriction alone, there was very little correction over the study period (<5 mmol/L over 72 hours), and the neurologic outcomes were much worse, with most of these patients either dying or entering a persistent vegetative state. Based on this and similar retrospective analyses, prompt therapy to rapidly increase the serum [Na+] represents the standard of care for treatment of patients presenting with severe symptoms of hyponatremia.

Brain herniation, the most dreaded complication of hyponatremia, is seen almost exclusively in patients with acute hyponatremia (usually <24 hours) or in patients with intracranial disease. In postoperative patients and in patients with self-induced water intoxication associated with marathon running, psychosis, or use of MDMA, non-specific symptoms such as headache, nausea, and vomiting or confusion can rapidly progress to seizures, respiratory arrest, and ultimately death or a permanent vegetative state as a complication of cerebral edema. Hypoxia from noncardiogenic pulmonary edema or hypoventilation can exacerbate brain swelling caused by the low serum [Na+]. Although usually self-limited, hyponatremic seizures may be refractory to anticonvulsants.

As discussed earlier, chronic hyponatremia is much less symptomatic as a result of the process of brain volume regulation. Because of this adaptation process, chronic hyponatremia is arguably a condition that clinicians feel they may not need to be as concerned about, which has been reinforced by the common usage of the descriptor asymptomatic hyponatremia for many such patients. However, as discussed previously, it is clear that many such patients very often do have neurologic symptoms, even if milder and subtler in nature. Consequently, all patients with hyponatremia who manifest any neurologic symptoms that could possibly be related to the hyponatremia should be considered candidates for treatment of the hyponatremia, regardless of the chronicity of the hyponatremia or the level of serum [Na+]. An additional reason to treat even asymptomatic hyponatremia effectively is to prevent a lowering of the serum [Na+] to more symptomatic and dangerous levels during treatment of underlying conditions (e.g., increased fluid administration via parenteral nutrition, treatment of heart failure with diuretics).

Currently Available Therapies for Treatment of Hyponatremia

Conventional management strategies for hyponatremia range from saline infusion and fluid restriction to pharmacologic measures to adjust fluid balance. Although the number of available treatments for hyponatremia is large, some are not appropriate for correction of symptomatic hyponatremia because they work too slowly or inconsistently to be effective in hospitalized patients (e.g., demeclocycline, mineralocorticoids). Consideration of treatment options should always include an evaluation of the benefits as well as the potential toxicities of any therapy and must be individualized for each patient. For all therapies, careful attention should be paid to recommendations for goals and limits of correction of the serum [Na+] in order to reduce the risk of the osmotic demyelination syndrome (ODS). Hypertonic saline. Acute hyponatremia presenting with severe neurologic symptoms is life threatening and should be treated promptly with hypertonic solutions, typically 3% NaCl ([Na+] = 513 mmol/L), as this represents the most reliable method to quickly raise the serum [Na+]. A continuous infusion of hypertonic NaCl is usually utilized in inpatient settings. Various formulas have been suggested for calculating the initial rate of infusion of hypertonic solutions, but until now there has been no consensus regarding optimal infusion rates of 3% NaCl. One of the simplest methods to estimate an initial 3% NaCl infusion rate utilizes the following relationship:

Patient’s weight (kg) × desired correction rate (mEq/L per hour) = infusion rate of 3% NaCl (mL/hour)

Depending on individual hospital policies, the administration of hypertonic solutions may require special considerations (e.g., placement in the intensive care unit, sign-off by a consultant), which each clinician needs to take into account in order to optimize patient care.

An alternative option for more emergent situations is administration of a 100-mL bolus of 3% NaCl, repeated twice if there is no clinical improvement in 30 minutes, which has been recommended by a consensus conference organized to develop guidelines for prevention and treatment of exercise-induced hyponatremia and adopted as a general recommendation by an expert panel. Injecting this amount of hypertonic saline intravenously raises the serum [Na+] by an average of 2 to 4 mmol/L, which is well below the recommended maximal daily rate of change of 10 to 12 mmol/L per 24 hours or 8 mmol/L per 24 hours for patients with increased risk factors for ODS (serum [Na+] ≤105 mmol/L), hypokalemia, advanced liver disease, malnutrition, or a history of alcoholism (see Fig. 10-8). Because the adult brain can only accommodate an average increase of approximately 8% in brain volume before...
herniation occurs, quickly increasing the serum [Na⁺] by as little as 2 to 4 mmol/L in acute hyponatremia can effectively reduce brain swelling and intracranial pressure. Isotonic Saline. The treatment of choice for depletional hyponatremia (i.e., hypovolemic hyponatremia) is isotonic saline ([Na⁺] = 154 mmol/L) to restore ECF volume and ensure adequate organ perfusion. This initial therapy is appropriate for patients who either have clinical signs of hypovolemia or in whom a spot urine Na⁺ concentration is lower than 20 to 30 mEq/L. Such patients often develop a free water diuresis (aquareasis) as their ECF volume is corrected, potentially leading to an overly rapid correction with increased risk of ODS, so the serum [Na⁺] and urine output should be followed carefully during the first 24 to 48 hours of therapy. However, isotonic saline is ineffective for dilutional hyponatremias such as SIADH, and continued administration of isotonic saline to a euclidean patient may worsen the hyponatremia or cause fluid overload. Although saline may improve the serum [Na⁺] in some patients with hypervolemic hyponatremia, the volume status will generally worsen with this therapy, so unless the hyponatremia is profound, both hypertonic and isotonic saline should be avoided.

Fluid Restriction. For patients with chronic hyponatremia, fluid restriction has been the most popular and most widely accepted treatment. When SIADH is present, fluids should generally be limited to 500 to 1000 mL/24 hours. Because fluid restriction increases the serum [Na⁺] by underreplacing the excretion of fluid by the kidneys, some have advocated an initial restriction to 500 mL less than the 24-hour urine output. When instituting fluid restriction, it is important for the nursing staff and the patient to understand that this includes all fluids that are consumed, not just water (Table 10-4). Generally the water content of ingested food is not included in the restriction because this is balanced by insensible water losses (perspiration, exhaled air, feces, etc.), but caution should be exercised with foods that have high fluid concentrations (such as fruits and soups). Restricting fluid intake can be effective when properly applied and managed in selected patients, but serum [Na⁺] is generally increased only slowly (1-2 mmol/L per day) even with severe fluid restriction. In addition, this therapy is often poorly tolerated because of an associated increase in thirst leading to poor compliance with long-term therapy.

Fluid restriction should not be used with hypovolemic patients and is particularly difficult to maintain in hospitalized patients with very elevated urine osmolalities secondary to high vasopressin levels; similarly, if the sum of urine Na⁺ and K⁺ exceeds the serum [Na⁺], most patients will not respond to a fluid restriction because an electrolyte-free water clearance will be difficult to achieve. These and other known predictors of failure of fluid restriction are summarized in Table 10-4; the presence of any of these factors in hospitalized patients with symptomatic hyponatremia make this less than ideal as an initial therapy. In addition, fluid restriction is not practical for some patients, particularly patients in intensive care settings who often require administration of significant volumes of fluids as part of their therapies. Such patients are candidates for more effective pharmacologic or saline treatment strategies.

Arginine Vasopressin Receptor Antagonists. Conventional therapies for hyponatremia, although effective in specific circumstances, are suboptimal for many different reasons, including variable efficacy, slow responses, intolerable side effects, and serious toxicities. But perhaps the greatest deficiency of most conventional therapies is that most of these therapies do not directly target the underlying cause of most dilutional hyponatremias, namely, inappropriately elevated plasma vasopressin levels. A new class of pharmacologic agents, vasopressin receptor antagonists, also known as vaptans, that directly block vasopressin-mediated receptor activation have recently been approved for treatment of euvolemic (U.S. and EU approval) and hypervolemic (U.S. approval) hyponatremia.

Conivaptan and all other vaptans, it is critical that the serum [Na⁺] is measured frequently during the active phase of correction of the hyponatremia—a minimum of every 6 to 8 hours for conivaptan but more frequently in patients with risk factors for ODS. If the correction exceeds 10 to 12 mmol/L in the first 24 hours, the infusion should be stopped and the patient monitored closely. Consideration should be given to administering sufficient water, either orally or as intravenous D5W, to avoid a correction of more than 10 to 12 mmol/L/day. The maximum correction limit should be reduced to 8 mmol/L over the first 24 hours in patients with risk factors for ODS (see Fig. 10-8). The most common side effects of conivaptan include headache, thirst, and hypokalemia.

Tolvaptan is a selective antagonist of vasopressin V₂ receptors. In contrast to conivaptan, the availability of tolvaptan in tablet form allows both short- and long-term use. Similar to conivaptan, tolvaptan treatment must be initiated in the hospital so that the rate of correction can be monitored carefully. In the United States, patients with a serum [Na⁺] lower than 125 mmol/L are eligible for therapy with tolvaptan as primary therapy; if the serum [Na⁺] is 125 mmol/L or higher, tolvaptan therapy is indicated only if the patient has symptoms that could be attributable to the hyponatremia and the patient is resistant to attempts at fluid restriction. In the European Union, tolvaptan is approved only for the treatment of euvolemic hyponatremia, but any symptomatic euvolemic patient is eligible for tolvaptan therapy, regardless of the level of hyponatremia or response to previous fluid restriction. The starting dose of tolvaptan is 15 mg on the first day, and

### Table 10-4

<table>
<thead>
<tr>
<th>General Recommendations for Employment of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction</th>
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<tr>
<td><strong>General Recommendations</strong></td>
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<tr>
<td>Restrict all intake that is consumed by drinking, not just water.</td>
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<tr>
<td>Aim for a fluid restriction that is 500 mL/day below the 24-hour urine volume.</td>
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<tr>
<td>Do not restrict sodium or protein intake unless indicated.</td>
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<tr>
<td><strong>Predictors of the Likely Failure of Fluid Restriction</strong></td>
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<tr>
<td>High urine osmolality (&gt;2500 mOsm/kg H₂O).</td>
</tr>
<tr>
<td>Sum of the urine Na⁺ and K⁺ concentrations exceeds the serum Na⁺ concentration.</td>
</tr>
<tr>
<td>24-hour urine volume &lt;1500 mL/day.</td>
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<tr>
<td>Increase in serum Na⁺ concentration &lt;2 mmol/L per day in 24 to 48 hours on a fluid restriction of ≥1 L/day.</td>
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the dose can be titrated to 30 mg and 60 mg at 24-hour intervals if the serum [Na\(^+\)] remains lower than 135 mmol/L or the increase in serum [Na\(^+\)] has been lower than 5 mmol/L in the previous 24 hours. As with conivaptan, it is essential that the serum [Na\(^+\)] is measured frequently during the active phase of correction of the hyponatremia, particularly in patients with risk factors for ODS. Goals and limits for safe correction of hyponatremia and methods to compensate for overly rapid corrections are the same as described previously for hypertonic saline and conivaptan (see Fig. 10-8). One additional factor that helps to avoid overly rapid correction with tolvaptan is the recommendation that fluid restriction not be used during the active phase of correction, thereby allowing the patient’s thirst to compensate for an overly vigorous aquaresis. Side effects of tolvaptan include dry mouth, thirst, increased urinary frequency, dizziness, nausea, and orthostatic hypotension.

Vaptans are not needed for treatment of hypovolemic hyponatremia, because simple volume expansion would be expected to abolish the nonosmotic stimulus to AVP secretion and lead to a prompt aquaresis. Furthermore, inducing increased renal fluid excretion via either a diuresis or an aquaresis can cause or worsen hypovolemia and hypotension in such patients. This possibility has resulted in the labeling of these drugs as contraindicated for hypovolemic hyponatremia. Importantly, clinically significant hypotension was not observed in either the conivaptan or tolvaptan clinical trials in euvoletic and hypervolemic hyponatremic patients. Although vaptans are not contraindicated with decreased renal function, these agents generally will not be effective if the serum creatinine is higher than 3.0 mg/dL. Recent findings of hepatotoxicity in a small number of patients on high doses of tolvaptan in a clinical trial of polycystic kidney disease has led to Food and Drug Administration (FDA) warnings on the use of vaptans in patients with liver failure and a recommendation that they not be used longer than 30 days, though this decision should be based on a risk-benefit analysis individualized for specific patients.

**Urea.** Urea has been described as an alternative oral treatment for SIADH and other hyponatremic disorders. The mode of action is to correct hypoosmolality not only by increasing solute-free water excretion but also by decreasing urinary sodium excretion. Doses of 15 to 60 g/day are generally effective; the dose can be titrated in increments of 15 g/day at weekly intervals as necessary to achieve normalization of the serum [Na\(^+\)]. It is advisable to dissolve the urea in orange juice or some other strongly flavored liquid to camouflage the bitter taste. Even if completely normal water balance is not achieved, it is often possible to allow the patient to maintain a less strict regimen of fluid restriction while receiving urea. The disadvantages associated with the use of urea include poor palatability, the development of azotemia at higher doses, and the unavailability of a convenient or FDA-approved form of the agent. Data suggest that blood urea concentrations may double during treatment, but it is important to remember that this does not represent renal impairment.

Reports of retrospective, uncontrolled studies suggest that the use of urea has been effective in treating SIADH in patients with hyponatremia due to subarachnoid hemorrhage and in critical care patients, and case reports have documented success in infants with chronic SIADH and the nephrogenic syndrome of inappropriate antidiuresis. More recent evidence from a short study in a small cohort of SIADH patients suggests that urea may have a comparable efficacy to vaptans in reversing hyponatremia due to chronic SIADH.

**Furosemide and NaCl.** The use of furosemide (20 to 40 mg/day) coupled with a high sodium intake (200 mEq/day) represents an extension of the treatment of acute symptomatic hyponatremia in selected cases. However, the efficacy of this approach to correct symptomatic hyponatremia both promptly and within accepted goal limits (see Fig. 10-8) is unknown.

**Hyponatremia Treatment Guidelines Based on Symptom Severity**

Although various authors and groups have published recommendations on the treatment of hyponatremia, no standardized treatment algorithms have yet been universally accepted. For all treatment recommendations, the initial evaluation includes an assessment of the ECF volume status of the patient, because treatment recommendations differ in hypovolemic, euvoletic, and hypervolemic hyponatremic patients. Euvolemic patients, mainly patients with SIADH, represent a unique challenge because of the multiplicity of causes and presentations of patients with SIADH. Recent expert opinion recommendations are based primarily on the neurologic symptoms of hyponatremic patients rather than the serum [Na\(^+\)] or on the chronicity of the hyponatremia, which is often difficult to ascertain. A careful neurologic history and assessment should always be done to identify potential causes for the patient’s symptoms other than hyponatremia, although it will not always be possible to exclude an additive contribution from the hyponatremia to an underlying neurologic condition. In this algorithm, patients are divided into three groups based on their presenting symptoms.

**Severe Symptoms.** Coma, obtundation, seizures, respiratory distress or arrest, and unexplained vomiting usually imply a more acute onset or worsening of hyponatremia, requiring immediate active treatment. Therapies that will quickly raise serum [Na\(^+\)] are required to reduce cerebral edema and decrease the risk of potentially fatal brain herniation.

**Moderate Symptoms.** Altered mental status, disorientation, confusion, unexplained nausea, gait instability, and falls generally indicate some degree of brain volume regulation and absence of clinically significant cerebral edema. These symptoms can be either chronic or acute but allow more time to elaborate a deliberate approach to choice of treatment.

**Mild or Absent Symptoms.** Minimal symptoms such as difficulty concentrating, irritability, altered mood, depression, and unexplained headache, or a virtual absence of discernible symptoms, indicate that the patient may have chronic or slowly evolving hyponatremia. These symptoms necessitate a cautious approach, especially when patients have underlying comorbid conditions.

Patients with severe symptoms should be treated with hypertonic (3%) NaCl as first-line therapy, followed by fluid restriction with or without vaptan therapy. Because overly rapid correction of serum [Na\(^+\)] occurs in more than 10% of patients treated with hypertonic NaCl, such patients are at risk for ODS unless carefully monitored. For this reason, some authors have proposed simultaneous treatment with desmopressin to reduce the rate of correction to only that produced by the hypertonic NaCl infusion itself. Whether sufficient clinical data eventually prove that this approach is both effective and safe in larger numbers of patients remains to be determined. Only one case of ODS has been reported in a patient receiving a vaptan monotherapy, and two abstracts have reported ODS when vaptans were used directly following hypertonic saline administration within in the same 24-hour period.
Consequently, no active hyponatremia therapy should be administered until at least 24 hours following successful increases in serum [Na⁺] using hypertonic NaCl.

The choice of treatment for patients with moderate symptoms will depend on their ECF volume status. Hypovolemic patients should be treated with solute repletion, either via isotonic NaCl infusion or oral sodium replacement. In euvoletic patients, typically with SIADH, will benefit from vaptan therapy, limited hypertonic saline administration, or in some cases urea, when available. This treatment can then be followed by fluid restriction or long-term vaptan therapy when the cause of the SIADH is expected to be chronic. In hypovolemic patients with heart failure, vaptans are usually the best choice because fluid restriction is rarely successful in this group, saline administration can cause fluid retention with increased edema, and urea can lead to ammonia buildup in the gastrointestinal tract if hepatic function is impaired. Although moderate neurologic symptoms can indicate that a patient is in an early stage of acute hyponatremia, they more often indicate a chronically hyponatremic state with sufficient brain volume adaptation to prevent marked symptoms from cerebral edema. Because most patients with moderate hyponatremic symptoms have a more chronic form of hyponatremia, guidelines for goals and limits of correction should be followed closely (see Fig. 10-8), and close monitoring of these patients in a hospital setting is warranted until the symptoms improve or stabilize.

Patients with mild or absent symptoms should be managed initially with fluid restriction, although treatment with pharmacologic therapy, such as vaptans or urea, may be appropriate for a wide range of specific clinical conditions, foremost of which is a failure to improve the serum [Na⁺] despite reasonable attempts at fluid restriction, or the presence of clinical characteristics associated with poor responses to fluid restriction (see Table 10-4). A special case is seen when spontaneous correction of hyponatremia occurs at an undesirably rapid rate as a result of the onset of a water diuresis, or aquaresis. This situation can occur following cessation of desmopressin therapy in a patient who has become hyponatremic, replacement of glucocorticoids in a patient with adrenal insufficiency, replacement of solutes in a patient with diuretic-induced hyponatremia, or spontaneous resolution of transient SIADH. Brain damage from ODS can clearly ensue in this setting if the preceding period of hyponatremia has been of sufficient duration (usually ≥48 hours) to allow brain volume regulation to occur. If the previously discussed correction parameters have been exceeded and the correction is proceeding more rapidly than planned (usually because of continued excretion of hypotonic urine), the risk of subsequent demyelination can be reduced by administration of hypotonic fluids, with or without desmopressin. Efficacy of this approach is suggested both from animal studies as well as case reports in humans, even when patients are overtly symptomatic. However, lowering the serum [Na⁺] after an initial overly rapid correction is only strongly recommended in patients who are at high risk of ODS, is considered optional in patients with low to moderate risk of ODS, and is unnecessary in patients with acute water intoxication (see Fig. 10-8).

Although this classification is based on presenting symptoms at the time of initial evaluation, it should be remembered that in some cases patients initially exhibit more moderate symptoms because they are in the early stages of hyponatremia. In addition, some patients with minimal symptoms are prone to develop more symptomatic hyponatremia during periods of increased fluid ingestion. In support of this, approximately 70% of 31 patients presenting to a university hospital with symptomatic hyponatremia and a mean serum [Na⁺] of 119 mmol/L had preexisting asymptomatic hyponatremia as the most common risk factor identified. Consequently, therapy of hyponatremia should also be considered to prevent progression from lower to higher levels of symptomatic hyponatremia, particularly in patients with a past history of repeated presentations for symptomatic hyponatremia.

Monitoring the Serum [Na⁺] in Hyponatremic Patients

The frequency of serum [Na⁺] monitoring is dependent on both the severity of the hyponatremia and the therapy chosen. All patients undergoing active treatment with hypertonic saline for symptomatic hyponatremia should have frequent monitoring of serum [Na⁺], urine output, and ECF volume status (every 2-4 hours) to ensure that the serum [Na⁺] does not exceed the limits of safe correction during the active phase of correction, because overly rapid correction of serum [Na⁺] will increase the risk of ODS. Patients treated with vaptans for moderate or mild symptoms should have serum [Na⁺] monitored every 6 to 8 hours during the active phase of correction, which will generally be the first 24 to 48 hours of therapy. Active treatment with any therapy should be stopped when the patient’s symptoms are no longer present, a safe serum [Na⁺] (usually >120 mmol/L) has been achieved, or the rate of correction has reached maximum limits of 10 to 12 mmol/L within 24 hours or 18 mmol/L within 48 hours or 8 mmol/L over any 24-hour period in patients at high risk of ODS (see Fig. 10-8). In patients with a stable level of serum [Na⁺] treated with fluid restriction or therapies other than hypertonic saline, measurement of serum [Na⁺] daily is generally sufficient, because levels will not change that quickly in the absence of active therapy or large changes in fluid intake or administration.

Future of Hyponatremia Therapy

Despite the many advances made in understanding the manifestations and consequences of hyponatremia, and the availability of effective pharmacologic therapies for the treatment of hyponatremia, it is obvious that we do not yet have a uniformly accepted consensus on how and when this disorder should be treated. In particular, the indications for the use of vasopressin receptor antagonists by regulatory agencies differ substantially around the world, and various treatment guidelines published to date also differ substantially on appropriate hyponatremia management. There are many reasons for this failure to achieve consensus, and until this is achieved via further clinical research studies, physicians must recognize the primary role that clinical judgment must continue to play in decision making about the management of hyponatremia in individual patients. Such judgments should take into account appropriate appraisals of evidence by authoritative experts in the field, the decisions of regulatory agencies that have based their approvals on a critical review of the efficacy and safety data for approved treatments for hyponatremia, and most important, the specialized needs of individual hyponatremic patients.

In the meantime, clinical trials using vasopressin receptor antagonists will enable investigators to answer some long-standing questions about the role of vasopressin V₂ receptor activation in producing antidiuresis in various physiologic conditions (e.g., regulation of sweat production), pathophysiologic states (e.g., hyponatremic patients without measurable vasopressin levels), and especially the potential reversibility of long-term adverse effects.
of hyponatremia that may account for the increased mortality rate and bone fracture rates of hyponatremic patients across multiple different comorbid conditions, as well as in subjects in the elderly community without known underlying diseases.

### Oxytocin

Study of the normal physiologic regulation of oxytocin secretion and action is complicated by the fact that secretion and function of oxytocin vary markedly among different experimental mammals. The sites of synthesis in the ovary and in tissues of the uterus also vary among species. It is difficult to study pregnant women and human tissue, so physiologic regulation of oxytocin secretion and function is less well known in humans than in other species. The classic roles of oxytocin are smooth muscle activation promoting milk let-down with nursing and uterine myometrial contraction at parturition.

### Lactation

A characteristic of all mammals is lactation, and all mammals secrete oxytocin to stimulate milk let-down associated with nursing. The other hormone critical to lactation is prolactin. Each of these pituitary/hypothalamic hormones is importantly influenced and regulated by gonadal steroid hormones. The milk-producing unit of the breast is the alveolar system with multiple clusters of milk-producing cells surrounded by specialized myoepithelial cells. The alveoli are directly connected to ductules and then ducts converge and lead to the nipple. Milk is synthesized in the glandular cells of the alveoli. Oxytocin receptors are localized on glandular cells and oxytocin in the systemic circulation acts on these receptors to cause myoepithelial contraction. Oxytocin also acts on myoepithelial cells along the duct to shorten and widen the ducts to enhance milk flow through the ducts to the nipple.

When an infant begins sucking at the breast an afferent signal is transmitted from the mechanoreceptors or tactile receptors in the breast to the spinal cord and eventually ascends to the oxytocinergic magnocellular neurons in the supraoptic nucleus and the paraventricular nucleus. Pulsatile release of oxytocin produces a pulsatile pumping action on the alveoli, which promotes maximum emptying of milk from the alveoli. The importance of oxytocin in maintaining milk secretion is demonstrated by transgenic mice with a knockout gene that inhibits oxytocin synthesis. These animals deliver their young normally and have normal milk production, but there is no milk release in the absence of vasopressin in patients with diabetes insipidus, even in those with traumatic section of the stalk.

### Parturition

The isolation of oxytocin was followed quickly by the description of oxytocin to stimulate uterine contractions, and this was followed shortly by clinical use of oxytocin as a uterotonic agent. Parturition in humans is much more complex than just the role of oxytocin. In all species the uterus must grow during pregnancy and estrogen is a promoter of this growth. Levels of oxytocin in humans is not well defined in pregnancy, but it is not reported to increase until the expulsive stage at term. The uterine myometrial cells have intrinsic contractile activity, but during pregnancy the uterus is maintained in a quiescent state by the actions of progesterone and relaxin (produced by the corpus luteum and decidual tissue). The initiation of labor is accomplished by a relative increase in estrogen activation and decrease in progesterone activation. Changes in oxytocin receptors and oxytocin produced by the placenta may be more important than levels of oxytocin in the circulation. During early labor there is an upregulation in the uterus of oxytocin receptor mRNA, and oxytocin receptor numbers increase. Oxytocin receptors are prominent in the fundus of the uterus, where they stimulate myometrial contraction, and in decidual cells, where they stimulate the production of prostaglandins. At parturition increased oxytocin activity in the fundus will push the fetus toward the cervix, which is thinned and relaxed by the effects of prostaglandins. Prostaglandins play a key role in an inflammatory process that is important in the uterus at parturition. Cytokines induce enzymes that digest extracellular matrix to soften and ripen the cervix. The role of progesterone in maintaining uterine quiescence is not only the action on oxytocin receptors but also by antagonizing the inflammatory response that is important for softening the lower uterus and cervix. Teleologically, it is appealing that the developing fetus when it reaches maturation would be a controlling factor in the initiation of labor. In sheep the action of the fetal hypothalamic/pituitary/adrenal axis is essential to initiating parturition, and in the human the role of CRH in human parturition has been extensively studied. CRH is synthesized by the placenta and increases exponentially throughout pregnancy with a peak during labor. CRH is secreted into the maternal plasma, where, as pregnancy advances, it stimulates ACTH and cortisol, although the feedback of cortisol on the pituitary and increased CRH binding proteins in plasma moderate the effect. In the fetus stimulation of pituitary ACTH and cortisol promotes maturation of the fetal lungs. The fetal lung secretes surfactant proteins and lipids into amniotic fluid, which enhances the release of cytokines and progression of the inflammatory response. In the human, parturition is a complicated cascade of events that interact with each other and feed forward with cross-stimulation. It is not surprising that a physiologic event as important to the species as pregnancy and parturition would have many redundant systems to assure survival of the species. An obvious thing to note in all of these discussions is the lack of understanding of the role of cysteine aminopeptidase (oxytocinase) in the physiology of pregnancy in the human. If this enzyme developed as a protective mechanism, then one would assume that oxytocin secretion by the neurohypophysis was increased throughout pregnancy, but the very presence of this enzyme and the obvious inability to do studies of the hypothalamus in vivo make this possibility uncertain.

There are three situations in pregnancy in which a pharmacologic role of oxytocin is of interest. The first situation
involves the most widely used role of oxytocin to induce and augment labor. This situation has received increased interest in an effort to decrease the number of and morbidity of cesarean sections. Oxytocin may be delivered alone or in combination with another pharmacologic agent such as propranolol or prostaglandins. The second area of interest is preterm labor with an effort to prevent premature labor by decreasing contractile activity of the uterus and inhibiting the inflammatory response. Peptide and nonpeptide oxytocin antagonists have been of especial interest to inhibit myometrial contractions, but widespread clinical use awaits the development of antagonists with better risk/benefit activity. The third pharmacologic interest in oxytocin is as a uterotonic to decrease postpartum hemorrhage associated with uterine atony. Postpartum hemorrhage is the major cause of maternal deaths worldwide and ranks second to embolism as a cause of maternal death in the United States. Mechanical options in the active management of the third stage of labor include cord traction to reduce the risk of retained placenta and uterine massage, which has been augmented by pharmacologic agents, most commonly oxytocin and ergotamine. Maternal deaths by postpartum hemorrhage are most significant in developing countries. Oxytocin is heat labile and requires a trained staff for appropriate administration, prompting a search for other agents. The most promising results have been reported with prostaglandin analogues, especially misoprostol.

Behavior

This chapter is about functions of vasopressin and oxytocin as traditional endocrine hormones secreted by the posterior pituitary. For further discussion related to these hormones in purported functions as neurotransmitters, especially with regard to influencing behavior, the reader is referred to Chapters 7 and 20.

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CHAPTER 10


